Pheochromocytoma as a rare cause of ventricular fibrillation

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This case report describes a rare cause of refractory ventricular fibrillation which was identified as a clinical manifestation of pheochromocytoma. It illustrates the pitfalls of diagnostics and surgical treatment of pheochromocytoma and the dilemma whether to implant in such patient an implantable cardioverter-defibrillator (ICD). Although the cause of cardiac arrest accompanying pheochromocytoma could be considered reversible, implantation was performed in this case due to presumed ventricular substrate with depressed left ventricular ejection fraction and with the prospect of potential recurrence of pheochromocytoma after surgery. To our best knowledge, only a few case studies of pheochromocytoma presenting with ventricular tachycardia have been reported. However, none of the published cases required prolonged cardiopulmonary resuscitation due to refractory ventricular fibrillation.

Key words: pheochromocytoma, refractory ventricular fibrillation, implantable cardioverter-defibrillator (ICD).

Feochromocytom jako neobvyklá příčina refrakterní fibrilace komor

Feochromocytom je vzácný neuroendokrinní nádor s výrazně variabilní klinickou manifestací a záchvatovitým průběhem. Prevalence feochomocytomu je velmi nízká a udává se přibližně u 0,1–0,6 % všech hypertoniků. Navzdory vzácnému výskytu hraje včasné stanovení diagnózy zásadní roli v další léčbě. Ta může být v některých případech životně důležitá. Typickou klinickou manifestací feochromocytomu je triáda bolestí hlavy, palpitací a zvýšeného pocení. Setrvalé komorové arytmie jsou popisovány vzácně. Přinášíme popis neobvyklého případu feochromocytomu manifestujícího se refrakterní komorovou fibrilací, která vyžadovala protrahovanou kardiopulmonální resuscitaci. Cílem této kazuistiky je ukázat záludnosti diagnosticko-terapeutického postupu a upozornit na vhodnost komplexního vyšetření ve specializovaném kardiovaskulárním centru u všech pacientů přeživších srdeční zástavu.

Klíčová slova: feochromocytom, refrakterní fibrilace komor, implantabilní kardioverter-defibrilátor.

Introduction

The majority of cases of out-of-hospital cardiac arrest due to ventricular fibrillation are associated with significant structural heart disease (most often coronary artery disease or idiopathic dilated cardiomyopathy) (1). Only a small proportion of cardiac arrests are manifestations of primary electric disease and/or other rare causes. Very rarely, any apparent cause can be reported, leading to the diagnosis of idiopathic ventricular fibrillation. In order to optimize clinical management of cardiac arrest survivor, evaluation should be optimally performed in a specialised cardiovascular centre. To our best knowledge, this is the first reported case of pheochromocytoma that triggered refractory ventricular which required prolonged cardiopulmonary resuscitation (CPR). Despite its rare occurrence, proper diagnosis of pheochromocytoma was crucial for subsequent management of the patient.

Case report

We present the case of a 57-year-old male with a history of diabetes mellitus type 2, arterial hypertension, paroxysmal atrial fibrillation and aortic valve replacement with mechanical prosthesis after an episode of infective endocarditis (25 years ago). He was admitted to our institution after prolonged out-of-hospital CPR for recurrent ventricular fibrillation (10 external DC shocks delivered over 30 minutes). Immediately after admission, therapeutic hypothermia was initiated and continued for 24 hours. Bedside transthoracic echocardiography showed moderate-to-severe left ventricular systolic dysfunction (LVEF 35 %, with diffuse wall motion abnormality). Mechanical aortic prosthesis was without dysfunction and no other pathology was found. Coronary angiography did not reveal any significant pathology and also brain computed tomography (CT) scan was normal. Toxicological laboratory results were negative. Besides severe hyperglycemia (35 mmol/l), laboratory findings

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Fig. 1. *CT scans of the abdomen. Imaging characteristics of a typical adrenal pheochromocytoma in the right adrenal gland*

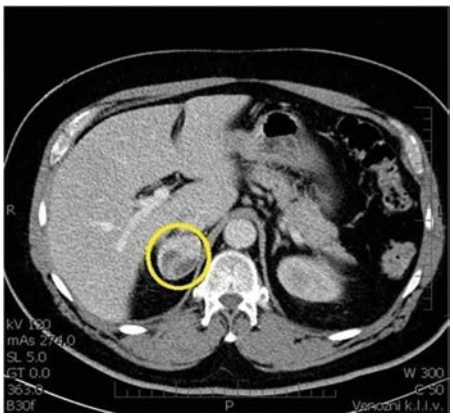
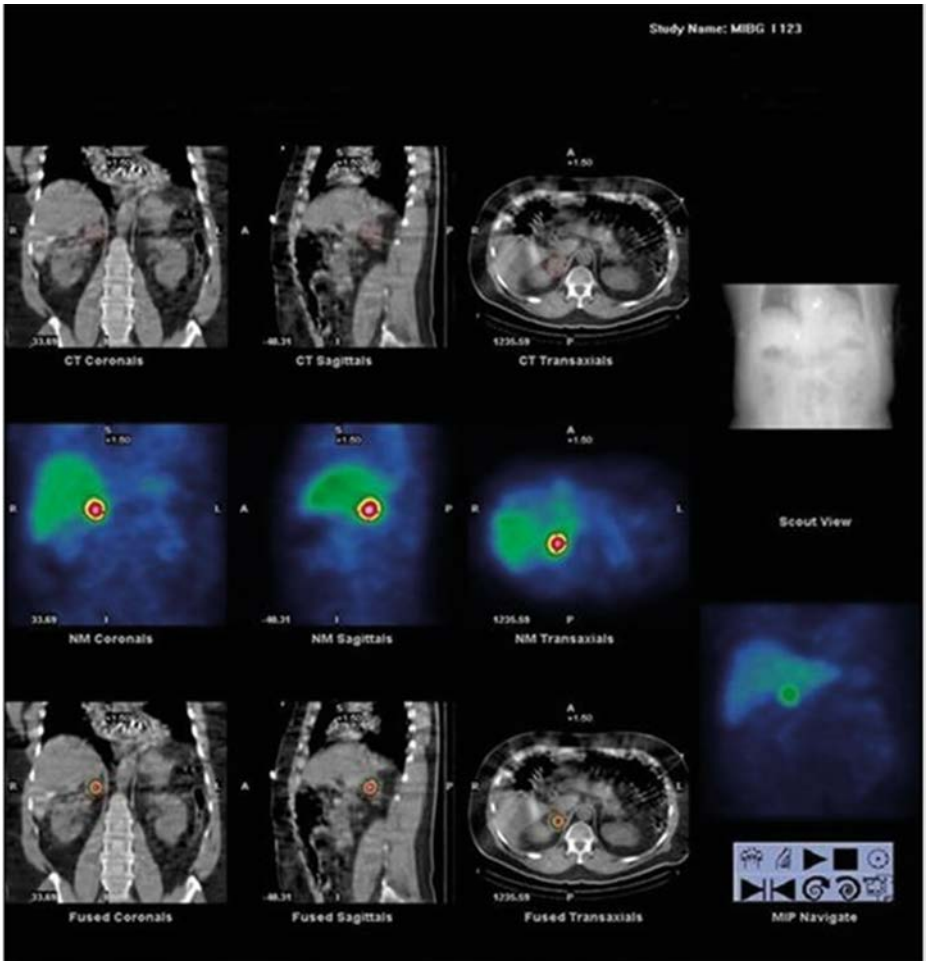


Fig. 2. *Merge of CT and MIBG scintigraphy. Fusion images help increase diagnostic certainty and are useful when planning surgery*



were consistent with multiple organ dysfunction syndrome. The patient recovered quickly at the intensive care unit, allowing for extubation on the third in-hospital day. Despite prolonged CPR (ROSC > 30 minutes), the patient survived without any neurological or cognitive deficit (CPC 1 – cerebral performance category 1 on 5 grades scale means a return to normal cerebral function and normal living). For persisting signs of renal insufficiency and pancreatic irritation, abdominal ultrasonography was performed. The main pathological finding was abnormal mass in the right adrenal gland. Plasma normetanephrine, chromogranin A and normetanephrine excretion levels (24-hour urinary collection) were highly elevated. An abdominal CT scan and metaiodobenzylguanidine (MIBG) scintigraphy confirmed diagnosis of hormonally active pheochromocytoma of the right adrenal gland (Figures 1, 2). Echocardiography performed two weeks later documented normalisation of left ventricular ejection fraction (55–60%).

The above clinical course and findings suggested very likely association between recurrent ventricular fibrillation and excessive catecholamine secretion. Several pieces of information supported this notion: 1) the patient was completely asymptomatic until cardiac arrest and had no signs of left ventricular dysfunction before; 2) no other cause of cardiac arrest was revealed and moderate left ventricular dysfunction immediately after the event normalized within two weeks. Given this scenario, one could consider the cause of ventricular fibrillation as reversible. However, previous history of cardiac surgery, transient left ventricular dysfunction and refractoriness of the electrical storm were taken into consideration as a reflection of potential morphological substrate. In addition, uncertainty about a success of adrenalectomy and/or risk of recurrence of tumor contributed to individualized decision to implant an ICD. One month later, after stabilisation and pharmacological preparation, the patient underwent right-sided adrenalectomy (the preferred laparoscopic approach was not possible due to obesity and anatomical conditions) (Figure 3). Metanephrine and chromogranin A levels normalised after surgery. In addition, improved compensation of diabetes mellitus and arterial hypertension was achieved. Six months after implantation a single episode of polymorphic ventricular tachycardia (heart rate 315/min) was documented and was terminated with the first DC shock (the patient reported just weakness without syncope). Chromogranin A levels were in normal range during this period. Patient remains stable and without further recurrences of ventricular arrhythmias during another 15 months of the follow up.

Discussion

This case report describes an extremely rare clinical manifestation of pheochromocytoma associated with out-of-hospital cardiac arrest due to refractory ventricular fibrillation triggered by excessive release of catecholamines. It illustrates the pitfalls of diagnostics and surgical treatment of pheochromocytoma and the dilemma whether to implant in such patient an implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death. Although the cause of cardiac arrest accompanying pheochromocytoma may be considered reversible, implantation was performed due to the history of previous valvular surgery and presumed pre-existing myocardial substrate as assessed by the presence of late potentials and depressed LVEF.

Pheochromocytoma is a rare neuroendocrine tumor with highly variable clinical expression and typical paroxysmal presentation. Symptoms occur in approximately 50% of patients, while the rest of the population is asymptomatic and tumor is found during autopsies (2). The prevalence of the tumor is approximately 0.1–0.6% in the hypertensive population. It originates predominantly from the adrenal medulla and only 10–20% from the extra-adrenal paraganglia (paragangliomas). Approximately 10–20% of pheochromocytomas

Fig. 3. *Pheochromocytoma after resection*

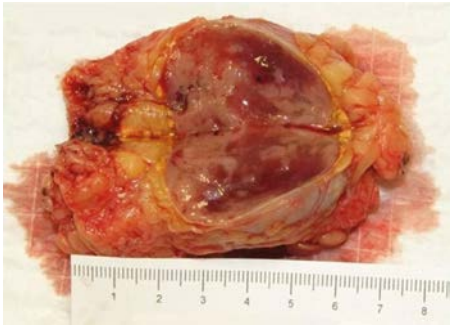
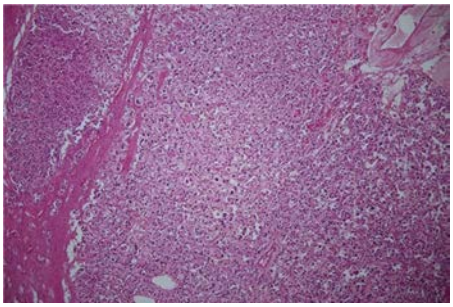


Fig. 4. *Histology. HE 100x. Polygonal cells in typical trabecular patterns*



are malignant, and genetic factors are implicated in 10–20% of cases, particularly in Von Hippel–Lindau syndrome, multiple endocrine neoplasia type 2 and neurofibromatosis (3). All of them have autosomal dominant inheritance, typically presenting at a younger age, where tumors are more likely to be bilateral.

Typical clinical presentation of pheochromocytoma consists of a triad: headache, palpitations and diaphoresis. However, other cardiac symptoms can also be present. In our case these warning symptoms were absent. The most common cardiac signs are labile hypertension and sinus tachycardia, secondary to high levels of circulating catecholamines. Sustained ventricular arrhythmias are rarely reported (3–9). There are case reports describing monomorphic or polymorphic ventricular tachycardias presented by a syncope. Some cases of sudden death have been reported in relation to pheochromocytoma (10), however, there is no report on refractory ventricular fibrillation that was successfully managed by prolonged CPR and repeated DC shocks.

Catecholamines produced by pheochromocytoma are metabolised within chromaffin cells. Norepinephrine is metabolised into normetanephrine and epinephrine into metanephrine. These metabolites are therefore used for diagnostic purposes. Plasma metanephrine testing has the highest sensitivity (96 to 100%) for detecting pheochromocytoma, but has lower specificity (85 to 89%). Specificity falls to 77% in patients older than 60 years (11). These conditions generate a high rate of false-positive test results. In comparison, 24-hour urinary collection of catecholamines and metanephrines has a sensitivity of 90% and a specificity of 98%. Another diagnostic possibility is to detect chromogranin A, which is an acidic monomeric protein stored and secreted together with catecholamines. Plasma levels of chromogranin A have been reported at 83% sensitivity and 96% specificity when identifying pheochromocytoma (12–14).

Biochemical diagnosis is typically followed by imaging studies in order to locate the tumor. Approximately 10 to 15% of catecholamine-secreting tumors are extra-adrenal (paragangliomas), while approximately 95% of catecholamine-secreting tumors are located in the abdomen (15). Abdominal ultrasound is usually the first examination, followed by computed tomography (CT) or magnetic resonance imaging (MRI). These latter methods may reveal occasionally adrenal masses without any clinical suspicion. In sporadic pheochromocytoma, both CT and MRI are equally sensitive (98 to 100%), but are only about 70% specific because of the higher prevalence of adrenal "incidentalomas" (16).

Typical imaging features include increased attenuation on CT (>20 Hounsfield units), high signal intensity on T2-weighted MRI, increased vascularity and cystic and hemorrhagic changes (15).

Importantly, larger tumors (more than 4 cm) are associated with an increased risk of malignancy. Familial pheochromocytoma and paragangliomas usually have multiple localisations. In these cases and when searching for metastases, MIBG scintigraphy is indicated. MIBG is a compound resembling norepinephrine, which is taken up by adrenergic tissue. Specificity is excellent (100%) with sensitivity at only 78%. Positron emission tomography (PET) is more sensitive than MIBG and CT/MRI, but due to its cost and availability is not routinely used. In our case, the dimensions of the well-vascularised hyperintense tumor were 38 × 35 × 43 mm.

Histological typical features are round or polygonal epithelioid cells arranged in compact cell nests or trabecular patterns (so-called Zellballen appearance) surrounded by a capillary network. Histological determination of malignancy is difficult. The case of malignant pheochromocytomas more frequently demonstrate invasion, large nests or diffuse growth, focal or confluent necrosis, high cellularity, increased mitotic activity, atypical mitotic figures, profound nuclear pleomorphism, hyperchromasia than the benign tumors (Figure 4).

The only curative method that ensures complete resolution of symptoms is complete resection of the tumor. Careful preoperative management is required to control blood pressure, correct fluid volume and prevent intraoperative hypertensive crises. Alpha blockade should be initiated 10–14 days preoperatively to allow for expansion of blood volume. The patient should undergo volume expansion with isotonic sodium chloride solution. Beta-blocker therapy should be started after adequate alpha blockade (usually after 2 days). If beta blockade is started prematurely, unopposed alpha stimulation can precipitate a hypertensive crisis. Laparoscopic adrenalectomy is now adopted as the procedure of choice. It is widely accepted that the laparoscopic approach ensures better visualisation of anatomically complex areas through smaller and less painful incisions. It is also associated with lower complication rates, less operative blood loss, less postoperative pain and an earlier return to activity. The hospital stay is shorter and overall costs lower. In addition, it provides better cosmetic results. On the other hand, laparoscopic adrenalectomy should be performed only when complete tumor resection with an intact adrenal capsule can be achieved. This is very important, as complete resection constitutes the only possibility of curing patients, and it should be taken into account that even small tumors may rarely be malignant. Conversion to an open procedure should be decided upon early, prior to disruption of the tumor capsule. Conversion (about 5%) to open surgery is recommended for large lesions (>8 cm) that are suspected to be malignant (17, 18). Also, in our patient, the initial laparoscopic procedure was converted into classical open surgery due to hepatomegaly, obesity and contact-bleeding fragile tissues.

Despite considering cardiac arrest in our patient potentially reversible, the secondary prophylactic implant of an ICD was thoroughly discussed among members of the heart team and with the patient. Taking into consideration previous heart surgery with an artificial valve, the depressed left ventricular ejection fraction and uncertainty about the natural course of the tumor after resection (19, 20), the decision was taken to implant prophylactically ICD. A single episode of recurrence of

ventricular arrhythmia several months after surgical resection of the tumor supported appropriate indication for the implant.

Conclusions

This case report emphasises the importance of comprehensive evaluation of all cardiac arrest survivors. In this case, pheochromocytoma was diagnosed as the most probable trigger for intractable ventricular fibrillation causing cardiac arrest. Rapid diagnosis of pheochromocytoma was based on a combination of imaging and laboratory methods, specifically catecholamines and their metabolites in blood and urine. Despite the fact that cardiac arrest could be considered potentially reversible in this situation, implantation of an ICD was recommended before resection of the tumor. Clinical recurrence of a single episode of ventricular arrhythmia necessitating therapy from the device several months later supported the individualised decision on implant.

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