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CASE REPORT
Heart failure

Recurrent angina and cardiac ischaemia as a presentation of pheochromocytoma: a case report

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Background We present a case of a pregnant patient with recurrent angina, in which her symptoms were initially attributed to coronary artery spasm. However, during follow-up, she was diagnosed as having pheochromocytoma, a rare neuroendocrine tumour.

Case summary The 35-year-old patient was admitted to the hospital because of chest pain and elevated cardiac troponins after the use of MDMA. Physical examination, electrocardiogram, echocardiography, coronary angiogram, and cardiac MRI were normal. Symptoms were attributed to coronary spasm, and a calcium antagonist was started. Ten months later, when 36 weeks pregnant, her symptoms returned. One week later, the patient was readmitted to the hospital with signs of acute left ventricular (LV) failure, highly elevated troponins, and severe global LV dysfunction. Urgent section caesarean was performed due to maternal morbidity and foetal tachycardia. During section, flushes and marked variability in blood pressure were noted. Laboratory metanephrines testing was performed. LV function recovered within 3 days without any therapeutic intervention. However, chest pain reoccurred, now accompanied with headaches, malignant hypertension, and accelerated idiopathic ventricular rhythms. (Nor)metanephrines tests were positive. A solid lesion in the right adrenal on CT scan confirmed the diagnosis of pheochromocytoma. Fluid repletion and alpha-blocker therapy were started. Due to persistent symptoms, urgent laparoscopic adrenalectomy was performed. Hereafter, the patient remained without symptoms.

Discussion A pheochromocytoma may present with recurrent angina and can result in a catecholamine-induced cardiomyopathy. It is important to timely recognize this diagnosis in order to minimize morbidity and mortality.

Keywords Pheochromocytoma • Catecholamine-induced cardiomyopathy • Angina with non-obstructive coronary arteries • Chest pain • Pregnancy • Case report

ESC curriculum 3.2 Acute coronary syndrome • 5.6 Ventricular arrhythmia • 6.4 Acute heart failure

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Learning points

- The absence of hypertension does not exclude the diagnosis of pheochromocytoma.
- Pheochromocytoma can result in an acute and transient catecholamine-induced cardiomyopathy, or chronic cardiomyopathy in case of persistent pheochromocytoma.
- In the current time, with increasing awareness of coronary artery spasm and microvascular dysfunction as a potential cause for chest pain, the authors would like to warrant that pheochromocytoma may mimic the presentation of myocardial infarction due to non-obstructive coronary artery disease.

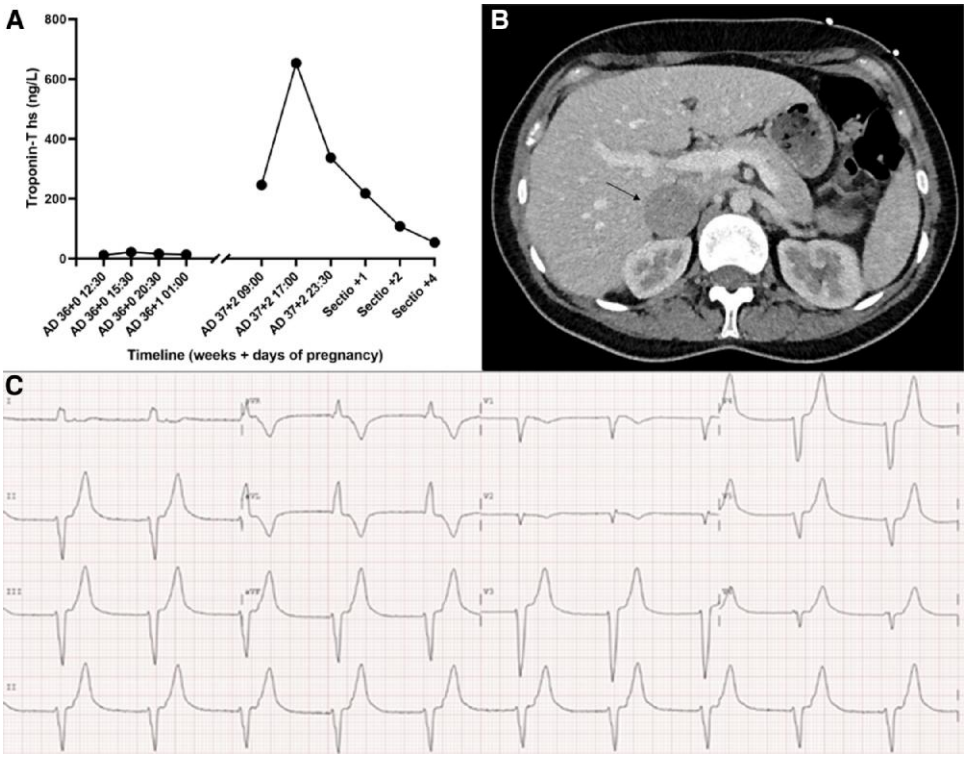
Introduction

Pheochromocytomas (PCCs), arising from the chromaffin cells within the adrenal medulla- and paragangliomas (PGLs) located extra-adrenal, are rare neuroendocrine tumours with an incidence of 0.8/100 000 patients per year.[1] We present a case of a pregnant patient with recurrent angina and elevated troponins, followed by acute heart failure, in which her symptoms were initially attributed to coronary artery spasm but turned out to be caused by pheochromocytoma.

Summary figure

Case presentation

A 36-year-old female, 36 weeks pregnant, presented at the obstetric clinic with chest pain. Her first symptoms started 10 months earlier, prior to pregnancy, after intake of methylene dioxymethamphetamine (MDMA). After MDMA, the patient experienced continuous substernal pressure without radiation, aggravated by exercise, deep inspiration, and supine position. She was pale, sweating, and experienced palpitations. At initial presentation, blood pressure was 99/76 mmHg and heart rate 90/min. Electrocardiogram (ECG) showed sinus rhythm with a prolonged corrected QT interval (QTc) of 473 ms without any ST-T segment deviation or PTa depression. QTc normalized spontaneously within 24 h.



(*A*) Time course of high sensitive troponin-T (reference range < 15 ng/L). (*B*) Computed tomography of the adrenal mass of the right adrenal gland of 3.7 cm (black arrow), with an intermediate washout. There were no signs of lymphatic or distant metastasis. (*C*) Electrocardiogram of accelerated idiopathic ventricular rhythm.

Laboratory tests showed normal D-dimer and rise-and-fall in troponin-I (max. 349 ng/L, reference range < 20 ng/L). Chest X-ray revealed no cardiopulmonary abnormalities. Echocardiogram showed normal left ventricular (LV) function and no pericardial effusion. Coronary angiogram showed normal coronary anatomy, without plaques/stenosis or coronary

dissection. Although severe radial artery spasm occurred, no spontaneous coronary spasm was observed and an additional acetylcholine provocation test was not performed. Cardiac MRI showed normal volumes and function, normal T1 and T2 values, and no late gadolinium enhancement. Thus, showing no signs of peri(myo)carditis, myocardial infarction, or cardiomyopathy, the patient was diagnosed myocardial infarction due to non-obstructive coronary artery disease (MINOCA) based on coronary artery spasm provoked by MDMA abuse. A calciumantagonist, nitroglycerine sublingual, and acetylsalicylic acid were prescribed. The patient was discharged from the hospital free of symptoms and never used using MDMA again/afterwards.

Two months after the start of medical treatment, drugs were stopped due to her pregnancy because of potential teratogenic effects. Notably, during the first months of pregnancy, the patient became symptom free.

However, at Week 36 of her pregnancy, the patient experienced recurrent chest pain (lasting from 15 min to 1.5 h) provoked by exercise and stress, along with sweating, paleness, and tingling of the fingers. Blood pressure was 93/58 mmHg. ECG and echocardiogram showed no abnormalities. Laboratory results showed mildly elevated high sensitive troponin-T (max. 22 ng/L, reference range < 15 ng/L), elevated D-dimer 1.27 mg/L (reference range < 0.5 mg/L), and normal TSH value (1.4 mE/L). Computed tomography (CT) scan showed no pulmonary embolisms. To avoid unnecessary radiation during pregnancy, coronary angiogram was not repeated. Again, her symptoms were attributed to MINOCA. As symptoms decreased during admission, patient was discharged.

One week hereafter, she was hospitalized with recurrent chest pain, worsening at inspiration. Physical examination showed a blood pressure of 95/55 mmHg, heart rate of 100/min, and transient low peripheral oxygen saturation levels up to 85% without signs of deep venous thrombosis. Troponin-T and D-dimer were elevated (max. 653 ng/L and 3.77 mg/L, respectively; Summary figure), but NT-proBNP was normal (127 ng/L, reference < 130 ng/L). ECG was normal. Based on the YEARS algorithm,[2,3] CT was repeated and showed no pulmonary embolism, but did show ground-glass opacities and septal thickening suggesting left-sided heart failure. Repeated echocardiography, though of limited image quality due to pregnancy and breast implants, showed severely reduced LV function without regional wall motion abnormalities or valvular disease (see Supplementary material online, *Video S1*). She was diagnosed as having acute left-sided heart failure. The differential diagnosis consisted of peripartum cardiomyopathy or MINOCA associated with coronary spasm. Due to maternal morbidity and foetal tachycardia, urgent caesarean section (C-section) was performed the same day. During C-section, flushes and a marked variability in blood pressure were noted, especially after administration of ephedrine. Metanephrines laboratory tests for pheochromocytoma were performed. C-section was uncomplicated, and the baby was born healthy. After C-section, the patient was transferred to the Coronary Care Unit for observation. Within 3 days after the C-section, LV function recovered completely and spontaneously, suggestive for Takotsubo, rather than MINOCA or coronary spasm. Patient remained free of symptoms for the first 3 days after C-section, but experienced progressive

Table 1 **(Nor)metanephrines laboratory tests**

Plasma levels	Results	Reference range
3-Methoxy-thyramine, nmol/L	0.20	0–0.10
Metanephrine, nmol/L	13.50	0–0.45
Normetanephrine, nmol/L	8.45	0–0.62

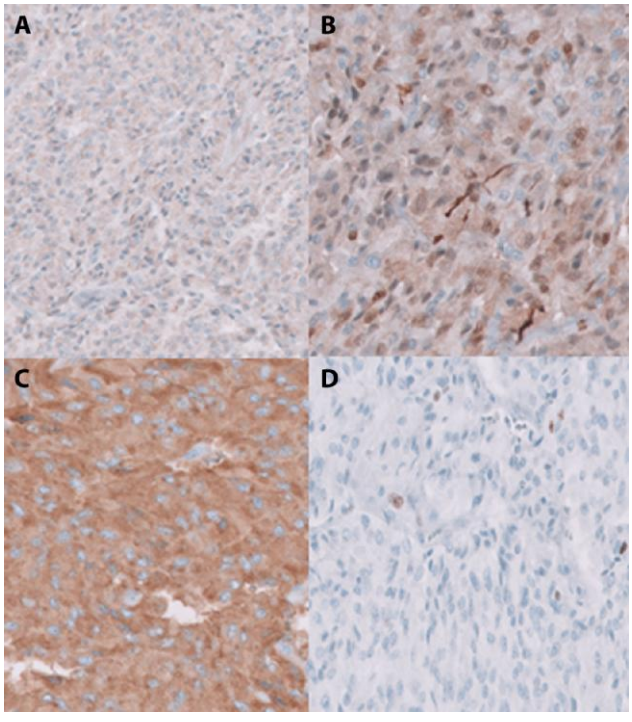


Figure 1 Histology of the removed adrenal mass. The lesional cells are weak positive (100%) for chromogranin (*A*), diffuse positive for S100 (*B*), and diffuse and strong positive (100%) for synaptophysin (*C*). Ki67 shows a proliferation of 3–5% (*D*).

recurrent episodes of chest pain thereafter, provoked by mobilization and a couple days later also in resting conditions. ECG showed no ST-T segment deviation. Blood pressures remained within normal limits during the first days after the C-section, however, she experienced 'spells' of severely increased blood pressures up to 250/100 mmHg with chest pain and severe headaches starting from Day 5 after C-section. Electrocardiographic monitoring showed concurrent episodes of accelerated idiopathic ventricular rhythms (AIVR, Summary figure) and premature ventricular contractions. At Day 5 after C-section, (nor) metanephrines tests turned positive (*Table 1*). CT of the abdomen revealed a solid lesion of the right adrenal gland of 3.7 cm in diameter, with an intermediate washout (Summary figure). The diagnosis of pheochromocytoma was confirmed. She was treated with an alpha-blocker and fluid supplementation (as dehydration is a potential worsening factor in pheochromocytoma). However, due to persistent symptoms, laparoscopic adrenalectomy was performed within 2 days after the CT scan. Thereafter, blood pressure remained within normal limits, and she remained symptom free. Histopathology of the resected adrenal gland confirmed the diagnosis pheochromocytoma (*Figure 1*).

Discussion

We present a 36-year-old pregnant patient who had recurrent angina without obstructive coronary artery disease, followed by a severe but transient LV dysfunction, in hindsight both explained by a pheochromocytoma.

PCCs/PGLs can secrete norepinephrine, epinephrine, or dopamine and other substances in varying amounts and, due to individual differences, symptomatology is highly variable.[4] Episodes with severe headache, palpitations, and diaphoresis are most characteristic for PCC/PGL, and are a result of adrenergic stimulation by the secreted catecholamines. However, this triad is only present in 24% of the cases.[5] These paroxysms are often accompanied with other symptoms like increased (or decreased) blood pressure, pallor, tremor, chest, and abdominal pain or less commonly flushing.[4] Symptoms can occur spontaneously, can be provoked by activities that compress the tumour (e.g. exercise, urination, and pregnancy), or can be provoked by certain types of medication/anaesthesia.[4,6]

In this case report, the likelihood of the presence of a pheochromocytoma increased significantly over time, after the recorded high blood pressures during the C-section and during episodes thereafter, underlining the importance of timely blood pressure measurements. It should be noted, however, that in this case, the patient also reported chest pain at moments where no high blood pressure was observed. Therefore, it should be noted that normal blood pressures during a paroxysm do not rule out PCCs/PGLs.[5] Besides hypertension, increased myocardial metabolism and catecholamine-induced coronary spasm are potential causes for angina/ischaemia in PCCs/PGLs.[7] In addition to more often seen brady- and tachyarrhythmia's, AIVR can also be present in pheochromocytoma.[8] Few cases have been reported showing pheochromocytoma can mimic MINOCA.[9–11]

Catecholamine-induced cardiomyopathy occurs in 10% of the patients with PCCs/PGLs.[12,13] Most frequently, it presents as an acute, transient Takotsubo-cardiomyopathy.[12,13] Neurovascular events can also be associated with Takotsubo syndrome.[14] Similar to stress-induced Takotsubo-cardiomyopathy, excess of catecholamine overloads β1-adrenoceptors increasing myocardial contraction and heart rate, thereby increasing myocardial oxygen demand. Simultaneously, stimulation of α1-adrenoceptors, microvascular alteration and calcium overload lead to oxygen-derived free radicals, (microvascular or epicardial) coronary spasm, and consequently to a decrease in myocardial oxygen supply.[12,13,15] This results in myocardial hypoxia leading to LV stunning and cell death.[12,13] Based on the clinical course in the presented case, it is most likely that the chest pain and troponin release were due to type 2 myocardial infarction, caused by a combination of hypertension and coronary spasms as a result of the pheochromocytoma.

In general, after relieve of catecholaminergic stress, LV function often recovers within weeks to months.[13] However, in case of unrecognized PCC/PGLs, prolonged catecholamine exposure induces inflammation, myocardial fibrosis, and necrosis potentially resulting in dilated (or hypertrophic) cardiomyopathy without reversibility.[12] Therefore, it is important to timely recognize this diagnosis in order to minimize morbidity and mortality.

Lead author biography

Arno van de Bovenkamp is a PhD candidate and cardiology resident at Amsterdam UMC.

Supplementary material

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

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author, if there is no conflict with the privacy of the patient.

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