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CASE REPORT
Cardiovascular imaging

Unusual case report of malignant pheochromocytoma presenting with STEMI

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Background Pheochromocytomas (PHEOs) are a group of tumours that leads to multiple symptoms and can induce hypercoagulability and promote thrombosis. Pheochromocytomas may also present without elevated serum and urinary markers. We aimed to provide tips and tricks for the diagnostic and therapeutic management of an unusual case of PHEOs.

Case summary Thirty-four-year-old woman with the unremarkable medical history presented with epigastric pain and dyspnoea. Electrocardiogram showed ST-segment elevation in the inferior limb leads. She underwent an emergency coronary angiogram, which showed a high thrombus burden in the distal right coronary artery. A subsequent echocardiogram demonstrated a 31 × 33 mm right atrial mass adhering to the inferior vena cava and abdominal computed tomography (CT) scan revealed a 113 × 85 mm necrotic mass in the left adrenal bed, with tumour thrombus extending proximally to the confluence of hepatic veins immediately inferior to the right atrium and distally to iliac vein bifurcation. Blood parameters, thrombophilia panel, vanillylmandelic acid, 5 hydroxy indole acetic acid, and homovanillic acid levels were normal. Tissue sampling confirmed the diagnosis of PHEOs. The surgical procedure was not planned due to the presence of metastatic foci on imaging, including positron emission tomography (PET)–CT. Anticoagulation with rivaroxaban and treatment with ^{177}Lu-DOTATATE-based peptide receptor radionuclide therapy (PRRT) was initiated.

Discussion The coexistence of arterial and venous thrombosis is extremely rare in patients with PHEOs. Multidisciplinary approaches are required for the care of such patients. Catecholamines likely contributed to the development of thrombosis in our patient. Early recognition of PHEOs is the key point to ameliorate clinical outcomes.

Keywords Pheochromocytoma • Case reports • Acute coronary syndrome • Pulmonary embolisms

ESC curriculum 2.2 Echocardiography • 3.2 Acute coronary syndrome • 9.5 Pulmonary thrombo-embolism • 9.4 Thrombo-embolic venous disease • 6.8 Cardiac tumours

Learning Points

- Pheochromocytoma (PHEO) may coexist with both STEMI, DVT, and pulmonary embolism.
- In addition, it may present with normal serum and urinary markers.
- Thus, clinical suspicion is of paramount significance in the management of PHEO.

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Introduction

Pheochromocytomas (PHEOs) occur in <0.2% of patients with hypertension.[1,2] A considerable number of PHEOs carry germline or somatic gene mutations, which are inherited in the autosomal dominant way. Clinical symptoms maybe resulting from the overproduction of catecholamines or a mass effect, amongst other complications. The most common presentation is hypertension, and the classic triad of symptoms is headaches, palpitations, and diaphoresis.[3] Diagnosis is often delayed since many patients have non-specific symptoms. Pheochromocytomas can have devastating consequences if not recognized and treated appropriately.[4] In such cases, PHEOs can lead to myocardial injury, acute coronary syndromes, and arrhythmias. Additionally, PHEOs can induce hypercoagulability and promote thrombosis.[5] Although the literature contains several reports of acute myocardial ischaemia related to PHEOs,[6] a case involving both the inferior vena cava, the right heart, the pulmonary artery, and the coronary artery was not reported, to the best of our knowledge. Here, we aim to emphasize tips and tricks for the diagnostic and therapeutic management of an unusual case of PHEOs.

Timeline

On admission	A coronary angiogram was performed on the patient after he had been diagnosed with STEMI. Cardiac arrest occurred during angiography linked to hypotension and ventricular fibrillation. The patient was defibrillated with 360 J, cardiopulmonary resuscitation was performed for 5 min due to asystole, 1 mg s.c. adrenaline was administered, and sinus rhythm was achieved. As a result of no reflow following stent deployment to the right coronary artery, tirofiban infusion was initiated
Day 1	An echocardiography showed a 31 × 33 mm right atrial mass adhering to the inferior vena cava
Day 2	Thrombolysis In Myocardial Infarction Grade 3 flow was achieved in control angiography after 2 days infusion of tirofiban
Day 3	The intracardiac mass was thought to be a thrombus. Anticoagulation with rivaroxaban was initiated in addition to dual antiplatelet therapy to prevent further embolic events. Diseases that may predispose to thrombosis were also investigated
Day 7	Possible cancer-induced thrombosis was suspected because of the palpable mass and ascites in her abdominal examination and a computed tomography (CT) scan of her abdomen and pelvis was obtained. Contrast-enhanced CT revealed a 11.3 cm enhanced necrotic mass in the left adrenal gland bed compatible with pheochromocytomas (PHEOs)
Day 9	Twenty-four-hour urine analyses were performed and revealed normal vanillylmandelic acid, 5 hydroxy indole acetic acid, and homovanillic acid levels
Day 13	Image-guided tissue sampling was obtained and histopathological analysis confirmed the final diagnosis of PHEOs
Day 17	Surgical procedure was not planned due to metastatic foci on both PET and contrast CT. In addition, the persistence of intense thrombus in the right heart and inferior vena cava despite intensive anticoagulant therapy
Day 20	Based on the above data, our patient was diagnosed with malign PHEOs and treatment with ^{177}Lu-DOTATATE-based peptide receptor radionuclide therapy was initiated
Day 30	Patient was discharged
Day 90	Sixty days after discharge, the patient was readmitted to intensive care with ascites and dyspnoea. The patient did not respond to treatment and died of septic shock due to nosocomial infections caused by vancomycin-resistant enterococci

Continued

Case presentation

An otherwise healthy 34-year-old woman with a body mass index of 20.2 has been referred to the emergency room for complaints of epigastric pain, dyspnoea, diaphoresis, nausea, and vomiting for the last 2 days. She had also lost 10% of her weight in the last 6 months. Abdominal examination revealed left flank pain and mild abdominal tenderness with ascites. A palpable painful mass was detected in the left upper abdomen. Pulse examination in all extremities was normal and no signs of cyanosis were observed. No murmur was heard during cardiac auscultation. On arrival, she was found to be hypotensive, with a blood pressure of 90/50 mmHg and a heart rate of 75 b.p.m. Moist rales were audible in the basal lung fields. Electrocardiogram was performed on the patient with discomfortable angina. Electrocardiogram showed ST-segment elevation in the inferior limb leads (see Supplementary material online, *Figure S1*).

The patient with hypotension received dopamine infusion and bolus saline replacement. As per standard protocol, she underwent an emergency coronary angiogram (*Figure 1A*), which showed high thrombus burden in the distal right coronary artery (RCA) [Thrombolysis In Myocardial Infarction (TIMI) Grade 0 flow], while all other segments of the epicardial coronary arteries (TIMI Grade 3 flow) were normal (*Figure 1C*). Due to no evidence of plaque formation, the lesion was considered spontaneous coronary artery dissection (SCAD). Initially, medical treatment was planned due to SCAD but cardiac arrest occurred during angiography linked with hypotension and ventricular fibrillation. The patient was defibrillated with 360 J, cardiopulmonary resuscitation was performed for 5 min due to asystole, 1 mg adrenaline was administered subcutaneously, and sinus rhythm was achieved. Therefore, predilatation with 2 × 15 mm balloon was performed to RCA lesion. The distal flow was not achieved despite the injection of glycoprotein IIb/IIIa (tirofiban) inhibitor and repeated balloon predilatation. Due to haemodynamic instability and no reflow, a 2.75 × 36 mm drug-eluting stent under pressure 14 atm was implanted into the RCA lesion. Tirofiban infusion and no-reflow protocol was planned for the patient who developed no reflow after stent deployment and was referred to the coronary intensive care unit. Thrombolysis In Myocardial Infarction Grade 3 flow was achieved in control angiography after 2 days infusion of tirofiban (*Figure 1B*).

An echocardiogram (ECHO) showed regional wall motion abnormalities hypokinesia of the inferior, posterior, and septal segments, an ejection fraction of 40%, and a 31 × 33 mm right atrial mass adhering to the inferior vena cava (*Figure 2A and B*). To exclude paradoxical embolism due to patent foramen ovale (PFO), we also performed a

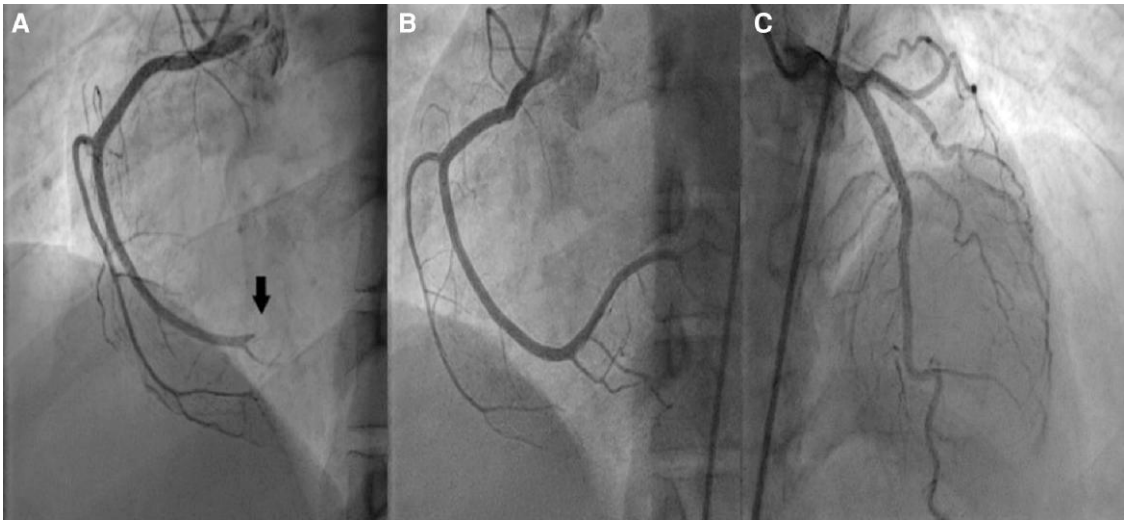

Figure 1 (*A*) Coronary angiogram showed high thrombus burden in the distal right coronary artery (Thrombolysis In Myocardial Infarction Grade 0 flow). (*B*) Thrombolysis In Myocardial Infarction Grade 3 flow was achieved in control angiography. (*C*) All other segments of the epicardial coronary arteries (Thrombolysis In Myocardial Infarction Grade 3 flow) were normal.

contrast ECHO. However, there was no evidence of a paradoxical embolism.

The intracardiac mass was thought to be a thrombus and anticoagulation with rivaroxaban was initiated in addition to dual antiplatelet (acetylsalicylic acid 100 mg p.o. qDay plus clopidogrel 75 mg p.o. qDay) therapy to prevent further embolic events. The diseases that may predispose to thrombosis were investigated in the patient without a past medical history. Haematological parameters, biochemical parameters, lipid profile, tumour markers, connective tissue markers, and thrombophilia panel were studied to explore rheumatological, hereditary, and thrombogenic diseases (see Supplementary material online, *Table S1*). All parameters were within normal limits except cancer antigen 125 (48.3 U/mL). Possible cancer-induced thrombosis was suspected because of the palpable mass and ascites in her abdominal examination and a computed tomography (CT) scan of her abdomen and pelvis was obtained. Contrast-enhanced CT revealed an 11.3 cm enhanced necrotic mass in the left adrenal gland bed (*Figure 3A* and *B*). Additionally, CT scan revealed tumour thrombus extending proximally up to the confluence of hepatic veins immediately inferior to the right atrium with distal extension to iliac vein bifurcation (*Figure 3C* and *D*). Venous Doppler of the bilateral lower extremity was unremarkable. Twenty-four-hour urine analyses revealed normal vanillylmandelic acid, 5 hydroxy indole acetic acid, and homovanillic acid levels (see Supplementary material online, *Table S1*). Image-guided tissue sampling was obtained and histopathological analysis confirmed the final diagnosis of PHEOs (*Figures 4A–D* and *5A–D*). Tumour cells with large, abundant, fine granular cytoplasm (*Figure 4A*), large, polygonal, nuclear pseudoinclusions (*Figure 4B*), granular, amphiphilic cytoplasm, pleomorphic nucleus, and marked nucleolus (*Figure 4C*), round-oval nucleus, prominent nucleolus (*Figure 4D*), and atypical mitosis support the diagnosis of PHEOs. Positive immune reaction with vimentin antibody (*Figure 5A*), positive immune reaction with CD56 antibody (*Figure 5B*), positive immune reaction with synaptophysin antibody (*Figure 5C*), and positive immunoreaction with MelanA antibody (*Figure 5D*) confirm PHEOs.

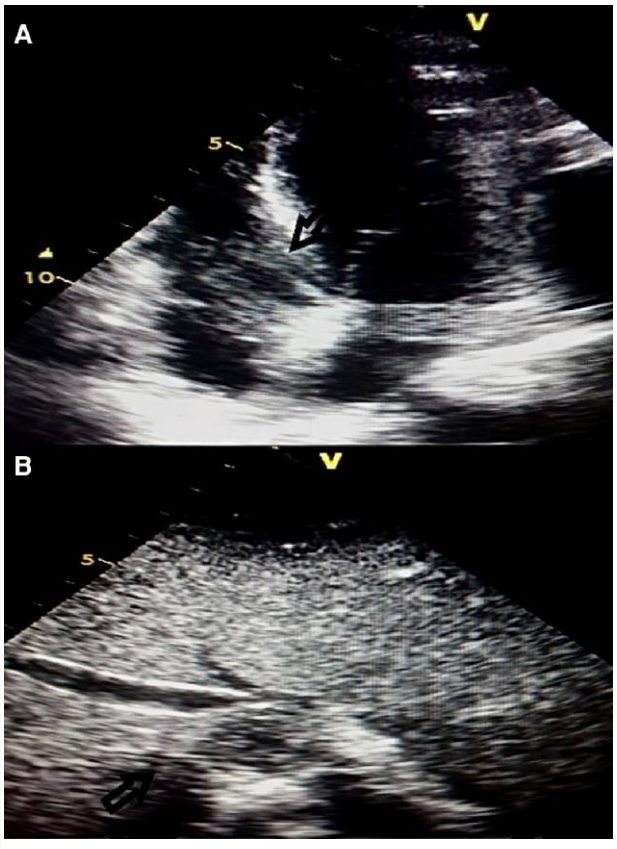

Figure 2 (*A* and *B*) An echocardiogram showed a 31 × 33 mm right atrial mass adhering to the inferior vena cava.

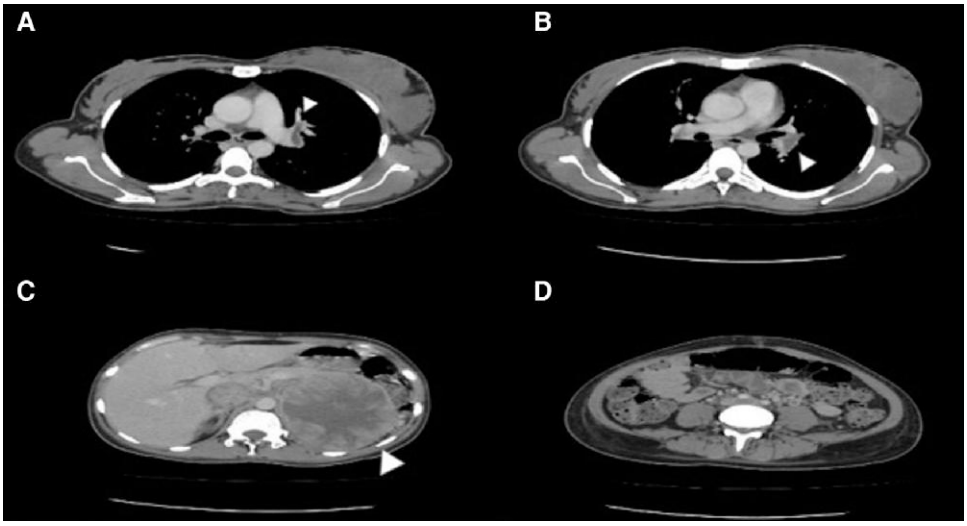

Figure 3 (*A* and *B*) Acute near-occlusive embolism in the left main pulmonary artery. Embolus was massive, involving bilateral pulmonary arteries, starting at the interlobar artery on the right side. There was evidence of right heart strain with a right to left ventricle ratio of 1.4. Hypodense peripheral consolidations with some ground glass changes in both lung bases were compatible with pulmonary infarctions. (*C*) Enhancing large round mass in the left adrenal bed inseparable from the left kidney and with spoke-wheel appearance and central necrosis. Also noted is an expansile occlusive thrombus involving the inferior vena cava. (*D*) Thrombus extended to the iliac bifurcation and bilateral common iliac veins. It was unclear if the thrombus extended beyond the level of common iliac veins due to potential contrast mixing artefacts.

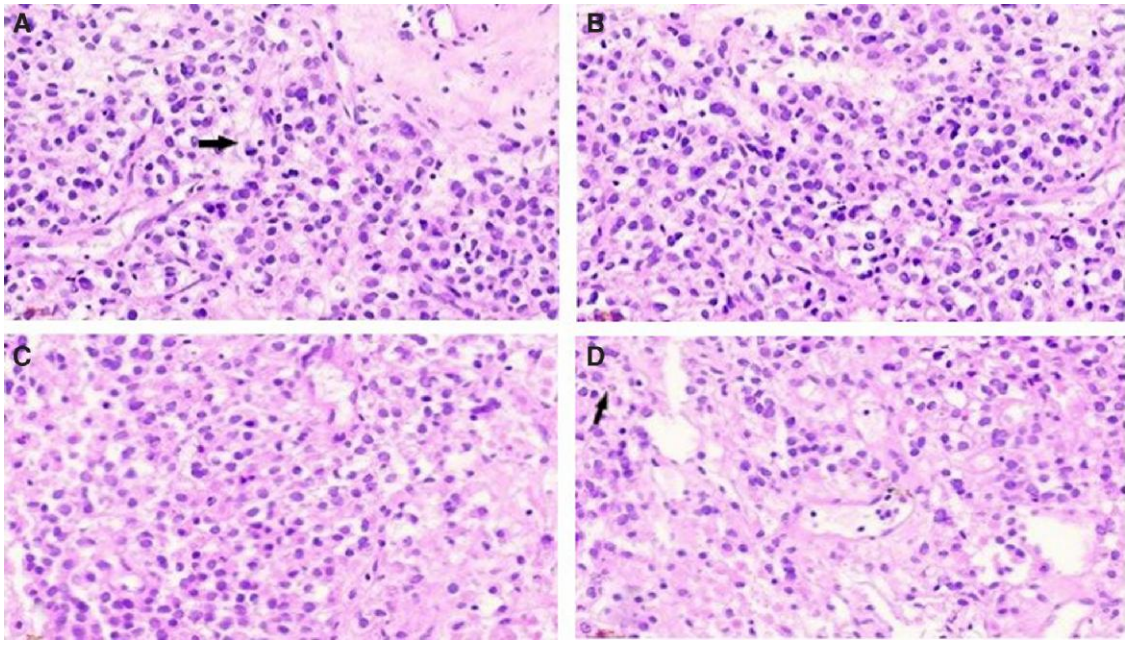

Figure 4 (*A–D*) High power (×400) view, haematoxylin–eosin staining, mass in the kidney, tru-cut biopsy. (*A*) Tumour cells with large, abundant, fine granular cytoplasm, (*B*) large, polygonal, nuclear pseudoinclusions, (*C*) granular, amphiphilic cytoplasm, pleomorphic nucleus, and marked nucleolus, and (*D*) round-oval nucleus, prominent nucleolus, (*A–D*) atypical mitosis (arrowhead).

The surgical procedure was not planned due to the presence of metastatic foci in both positron emission tomography (PET) and contrast CT. In addition, the persistence of intense thrombus in the right heart and inferior vena cava despite intensive anticoagulant therapy.

Based on the above data, our patient was diagnosed with malign PHEOs. ^{177}Lu-DOTATATE-based peptide receptor radionuclide therapy (PRRT) is a promising therapy for metastatic and/or inoperable PHEOs and paragangliomas (PPGL). Treatment with ^{177}Lu-DOTATATE-based

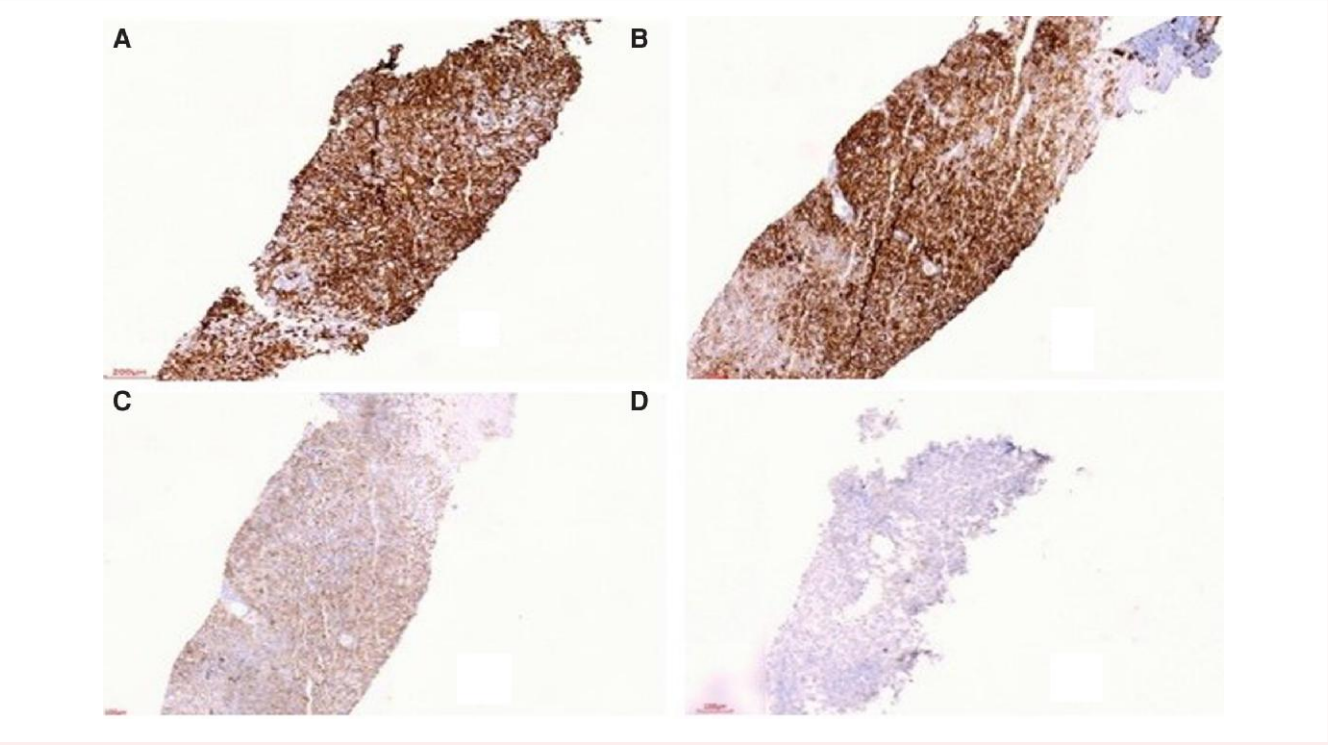

Figure 5 (*A–D*) Immunohistochemical study. (*A*) Diffuse strong positive immune reaction with vimentin antibody (×200), (*B*)- diffuse strong positive immune reaction with CD56 antibody (×200), (*C*) diffuse positive immune reaction with synaptophysin antibody (×200), and (*D*) suspected positive immunoreaction with MelanA antibody (×100).

PRRT was initiated. However, the patient did not respond to treatment and died of septic shock due to nosocomial infections caused by vancomycin-resistant enterococci.

Discussion

In this report, we describe a patient with ST segment elevated myocardial infarction (STEMI) DVT: and a large left adrenal PHEOs. As far as we know, no prior cases were reported to have such a dense thrombus burden in the coronary artery, pulmonary arteries, and venous system.

The number of STEMI cases associated with PHEOs in the literature is limited. Chen *et al.*[7] described a case of PHEOs crisis with STEMI. In this case, the risk factors that could predispose to atherosclerosis had shown no indication of coronary plaque formation angiographically. Laboratory measurement excluded thrombogenic diseases.

In addition to multifactorial mechanisms, PHEOs play a key role in thrombosis. Catecholamine hormones may reduce coronary blood flow or cause coronary spasms or induce hypercoagulation to promote thrombosis. Malignancies can also lead to hypercoagulation. It is often the result of inflammatory cytokines, coagulation proteins, and procoagulants secreted by tumour cells.[8] Venous thrombosis in malignant renal and/or adrenal tumours is not uncommon. Adrenocortical carcinoma (ACC) is a rare malignancy that can lead to venous thrombosis.[9] However, our case was not compatible with ACC, both radiologically and histopathologically.

Venous thrombosis occurring in patients with PHEOs has been reported previously in a few cases. Kota *et al.*[10] described the abnormality of the inferior vena cava anatomy which led to thrombosis and emphasized the importance of evaluating the inferior vena cava anatomy with magnetic resonance imaging or CT. Poudyal *et al.*[11] described a case of PHEOs in a postpartum woman which is a well-known cause of hypercoagulability. One of the conditions that makes the case of 'Poudyal *et al.*' interesting is the presence of marker-negative PHEOs and unremarkable metanephrine levels. In our case, pheochromocytoma markers in the 24 h urine were also within the normal range. In such cases, it was very difficult to label the adrenal tumour as PHEOs. Heavner *et al.*[12] reported 9% of PHEOs to be marker-negative in their series. In such cases, 123I-MIBG or 18F-FDG PET is recommended to avoid missing PHEOs. 123I-MIBG, 18F-FDG PET scan was performed as suggested by Cantalamessa *et al.*[13] 123I-MIBG, 18F-FDG PET–CT showed increased radiotracer uptake and metastatic foci which supported malignant PHEOs.

Hyperviscosity can cause thrombosis. Polycythaemia is also one of the well-known causes of hyperviscosity. Shulkin *et al.*[14] showed an association of polycythaemia with PHEOs. Polycythaemia can be observed uncommonly in cases of PHEOs because of erythropoietin secretion by the tumours. In our case, the JAK 2 gene mutation was negative and the platelet count was within the normal range.

In patients with PHEOs, STEMI can also occur as a result of SCAD, venous thrombus migration through PFOs, and arterial thrombosis.[8] Spontaneous coronary artery dissections account for <1% of acute myocardial infarctions. They occur most commonly in women and most often between the ages of 47 and 53 years. They may be associated with an underlying disorder such as fibromuscular dysplasia and other non-coronary arterial abnormalities, and are usually treated medically.[15] Paradoxical embolism is a well recognized in the setting of acute ischaemic stroke and a scarcely reported cause of myocardial infarction.[16]

The management of PHEOs are crucial, especially in the case of malignant PHEOs. There is no effective cure for PHEOs, once metastases occur. Although reliable data suggesting improved survival after surgical

debulking are lacking, surgery can plan for palliation, especially to treat local complications related to metastases. It can also reduce the burden of chromaffin tissue and hormonal activity. Surgical debulking may also be used to strengthen the efficacy of other therapies. However, no evidence exists that this therapeutic approach improves the survival of patients in case of malignant PHEOs.[17] Besides surgical treatment, chemotherapy and radiotherapy are also effective treatment regimens. In case of a sufficient uptake of 123I-MIBG treatment with targeted radiation therapy, the use of 131I-MIBG is an option.[18] Chemotherapy regimens are another treatment option. Most of the published regimens consist of alkylating agents such as cyclophosphamide, which has been shown to result in a significant reduction in catecholamine excretion.[19] Last but not least, new targeted therapies such as a radiotherapeutic approach with radiolabelled somatostatin analogues like ^{177}lutetium (Lu)-DOTA-octreotide may provide palliative benefits.[20]

Conclusion

Our experience with this patient was unique because she did not exhibit typical symptoms making an initial diagnosis difficult. Pheochromocytomas may coexist with STEMI, deep venous thrombosis, and pulmonary embolism and may also present without elevated serum and urinary markers. Thus, clinical suspicion is of paramount importance in the management of PHEOs.

Lead author biography

He graduated from Istanbul University Cerrahpaşa Faculty of Medicine in 2011. He completed his cardiology residency at Dicle University Faculty of Medicine/Diyarbakır/Turkey in 2016. Professionally interested in interventional cardiology and pacemakers. He enjoys spending time with his family, reading novels, solving chess puzzles, and listening classical music, especially MOZART.

Supplementary material

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

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

Consent: Written informed consent was obtained from the patient for publication of this case report in accordance with COPE guidelines. A copy of the written consent is available for review by the journal Editor.

Conflict of interest: None declared.

Funding: None declared.

Ethics approval: Our institution does not require ethical approval for reporting individual cases or case series.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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