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CASE REPORT
Other

Innovative approach to a functional mediastinal paraganglioma with anomalous coronary supply: a case report

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Background Mediastinal paragangliomas (PGs) are rare and particularly challenging neuroendocrine tumours. Clinical presentation is heterogeneous and tumour resection can be challenging due to bleeding and the risk of catecholamine surges in functional tumours.

Case Summary A 36-year-old man with multiple cardiovascular risk factors was admitted with subacute heart failure. Investigations revealed a large non-metastatic functional mediastinal PG irrigated mainly by a left circumflex coronary anomalous feeder branch. The surgical risk was deemed very high due to patient comorbidities, tumour vascularization, and close relation to major thoracic structures. A multidisciplinary team decided to perform embolization of the anomalous coronary branch followed by peptide-receptor radionuclide therapy with 177-LuDOTATE aiming to decrease tumour size and perioperative risk. Follow-up studies showed a reduction in tumour vascularization, size, and hormonal production.

Discussion The innovative strategy of combining embolization of the anomalous feeder branch with radionuclide therapy proved to be a promising approach.

Keywords Mediastinal paraganglioma • Coronary embolization • Radionuclide therapy • Neuroendocrine tumour • Case report

Learning points

- Functional mediastinal paragangliomas (PGs) are extremely rare. They pose serious challenges in surgical resection due to the risk of catecholamine surges and extensive blood loss.
- Embolization of the feeding artery prior to resection is a promising strategy to minimize perioperative bleeding in thoracic PGs.
- Peptide-receptor radionuclide therapy is increasingly recognized as an effective therapy in neuroendocrine tumours and is a solid option for patients with tumours considered inoperable.

Introduction

Mediastinal paragangliomas (PGs) are extremely rare neuroendocrine tumours. Clinical presentation varies and tumour resection can be challenging due to bleeding and hormonal secretion during tumour manipulation.[1–3] In patients with very high surgical risk, innovative adjunctive strategies should be considered to try to reduce complications during surgery.

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Timeline

Clinical presentation (Day 0)	• 36-year-old man with: multiple cardiovascular risk factors, schizophrenia • Symptoms at presentation: dyspnoea, palpitations, and atypical chest pain • Initial evaluation in the emergency room: rapid atrial flutter, signs of congestive heart failure
Imaging studies (Days 0–1)	• Transthoracic echocardiography: extrinsic compression on the left atrium, moderate systolic dysfunction • Coronary angiography: no epicardial coronary disease, large vascularized mass supplied mainly by an anomalous branch from the left circumflex coronary • Contrast computed tomography (CT): mediastinal mass of 61 × 53 × 33 mm
Functional studies (Days 1–5)	• Hormonal analysis: elevation of 24-h urinary and plasmatic normetanephrine values • Whole-body 123-MIBG scintigraphy: isolated enhanced uptake in the mediastinum
Diagnosis	• Large non-metastatic functional mediastinal paraganglioma with a left circumflex coronary anomalous feeder branch
Therapeutic approach (Months 0–1)	• Mutidisciplinary discussion: Initial surgical risk considered high • Three-step strategy to decrease risk: α and β blockade, embolization of the anomalous coronary branch, radionuclide therapy (1 cycle every 3–5 months)
Follow-up (Months 1–18)	• Outpatient consult (monthly): symptomatic improvement, no arrhythmia recurrence • Contrast CT (1 and 11 months after embolization): successful embolization, slight decrease in tumour size • Echocardiography (6 months after presentation): improvement in left ventricular function • Death (suicide) before surgery (18 months after initial presentation)

Case presentation

A 36-year-old man presented to the hospital with subacute onset heart failure, palpitations, and atypical chest pain. He had schizophrenia (with an admission 10 years prior for paranoia and suicidal behaviour) and several cardiovascular risk factors, including hypertension, smoking habits, dyslipidaemia, and obesity (body mass index 48 kg/m^2). His medication included bisoprolol 2.5 mg o.d., ramipril 5 mg o.d., simvastatin 20 mg o.d., metformin 1000 mg b.i.d., lamotrigine 25 mg o.d., risperidone 4.5 mg o.d., and lorazepam 2.5 mg o.d.

Upon initial examination, he was tachycardic at 150 b.p.m., had a blood pressure of 110/55 mmHg, and a peripheral oxygen saturation of 90%. Heart sounds were rapid with no murmurs, jugular venous pressure was raised at 45°, there were bilateral pulmonary rales and pedal oedema. Electrocardiogram revealed rapid atrial flutter (150 b.p.m.) and non-specific ST changes (*Figure 1*). A transoesophageal echocardiogram was done in the emergency room and excluded left atrial appendage thrombus, allowing for safe cardioversion (1 synchronized 150 Joules shock) that successfully reverted the patient back to sinus rhythm. The transthoracic echocardiogram performed at the echo laboratory disclosed an extrinsic compression on the left atrium and left ventricular (LV) moderate systolic dysfunction with global hypokinesia (Supplementary material online, *Video S1*).

Given the patient's risk factors and clinical presentation, a coronary angiography was performed to evaluate for coronary disease. There was no epicardial coronary disease, but the angiography showed a large vascularized mass located posteriorly to the heart. The mass was supplied mainly by an anomalous feeder branch arising from the left circumflex coronary (*Figure 2*; Supplementary material online, *Video S2*).

Contrast computed tomography (CT) scan revealed a large mediastinal mass (61 × 53 × 33 mm) with heterogeneous arterial-phase enhancement and compression of the left atrium (*Figure 3A*). The poorly defined borders of the mass suggested local invasion of the pulmonary arteries and the pericardium. These CT findings raised the suspicion of a PG. There were no other masses or suspicious ganglia in the thoracic, abdominal or pelvic compartments.

Hormonal analysis showed significant elevation of 24-h urinary and plasmatic normetanephrine values, revealing that this was a functional(catecholamine-secreting) PG. A subsequent whole-body 123-MIBG scintigraphy confirmed an isolated enhanced uptake in the mediastinum.

The final diagnosis was consistent with the presence of a large non-metastatic functional mediastinal PG, with a left circumflex coronary anomalous feeder branch. Catecholamine secretion and direct mass effect were the most likely causes for atrial flutter and subsequent tachycardiomyopathy.

Anticoagulation with rivaroxaban (20 mg o.d.) was started. Alpha and beta blockade was achieved by adding the alpha-blocker phenoxybenzamine (10 mg initially slowly titrated until 30 mg/day) to the selective beta-blocker bisoprolol (2.5 mg o.d.). The case was subsequently discussed at a multidisciplinary meeting with the cardiology and neuroendocrine thoracic tumours teams.

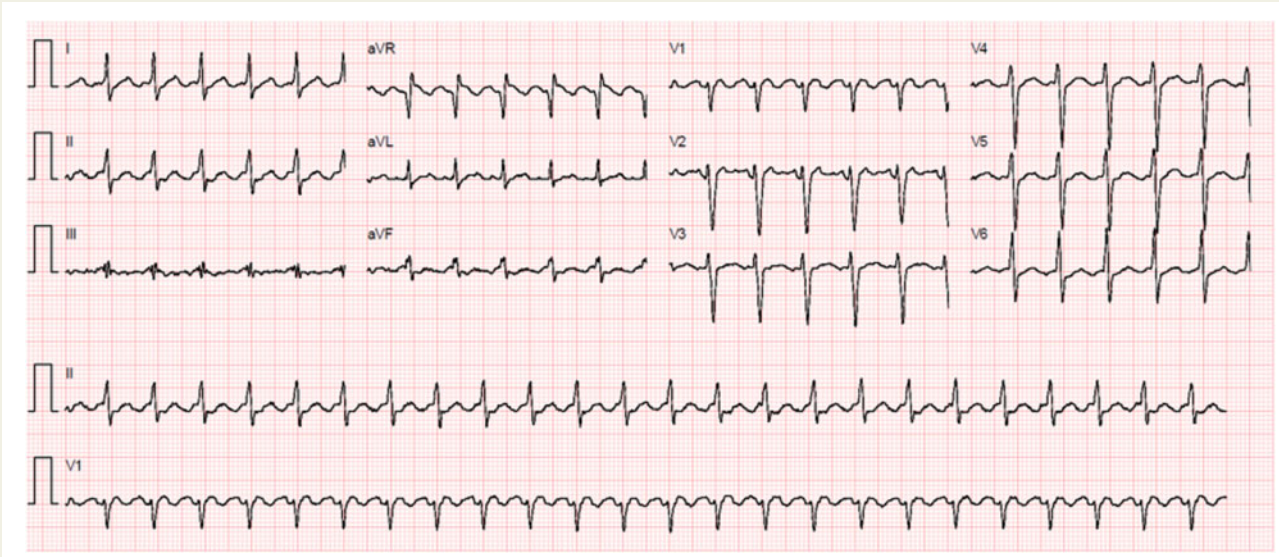


Figure 1 Electrocardiogram showing atrial flutter at 150 b.p.m. and non-specific ST-T changes.

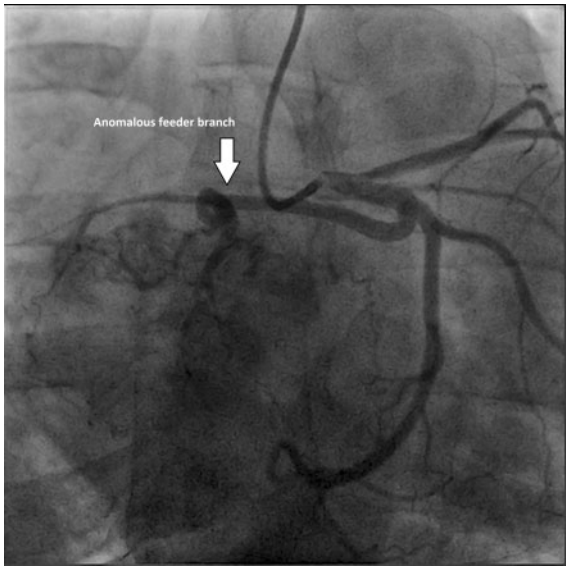


Figure 2 Coronary angiography (right cranial view) showing the left circumflex coronary anomalous feeder branch (arrow).

Surgical risk was deemed high due to (i) patient comorbidities (metabolic syndrome, LV dysfunction, and schizophrenia), (ii) tumour vascularization and proximity to major thoracic structures, and (iii) risk of catecholamine surges. The team's approach to try to optimize the patient prior to surgery, namely by trying to decrease tumour size and the risk of perioperative complications, consisted of three steps. The first was alpha and beta blockade, the second was to perform embolization of the anomalous coronary branch, and the third was peptide-receptor radionuclide therapy with 177-Lu-DOTATE. The patient's 68-Galium-DOTANOC positron emission tomography scan showed high expression of somastostatin receptors (*Figure 4*), making him a good candidate for radionuclide therapy.

Cardiac catheterization was performed via radial artery. For the embolization procedure, the interventional cardiologists used the *EBU 3.5–4* (Medtronic®) guiding catheter, the *BMW* guidewire (Abbot®), and the microcatheter *finecross* (Terumo®). Two hydrocoils (AZUR®) were deployed in the anomalous branch of the circumflex artery achieving significant reduction in distal flow (Supplementary material online, *Video S3*). Subsequently, the patient underwent radionuclide therapy with 177-Lu-DOTATE and completed two cycles during the following year (1 cycle every 3–5 months).

A CT coronarography performed 1 month after the procedure and confirmed the successful embolization of the anomalous branch. A second follow-up CT was performed after the second cycle of radionuclide therapy (11 months after embolization) (*Figure 3B*). It confirmed a reduction both in tumour vascularization and size (from 61 × 53 × 33 mm to 59 × 50 × 29 mm). The patient was followed monthly via outpatient consultations. His symptoms slowly improved and there was no evidence of arrhythmia recurrence. Echocardiography was done every 6 months and showed an improvement in LV function (39–50% in LV ejection fraction by Simpson's biplane). Hormonal analysis revealed a decrease in catecholamine levels [plasmatic normetanephrine (upper limit of normal < 983): initial value: 4530 pmol/L, at 12 months: 4420 pmol/L; urinary normetanephrines (normal-range: 480–2424): initial value 10454 nmol/day, at 12 months: 8894 nmol/day]. Genetic testing for SDHAF2, SDHB, SDHC, SDHD, MAX, TMEM127, and VHL genes was negative.

The adjunctive strategies to reduce surgical risk showed positive results. Unfortunately, the patient expired due to unrelated causes (suicide) before the procedure (18 months after initial presentation).

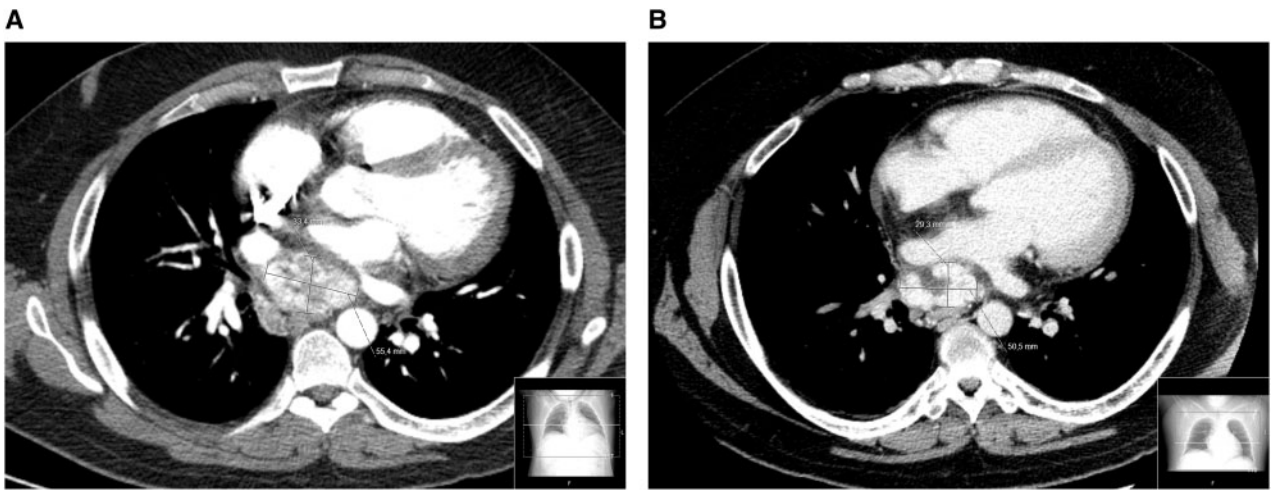


Figure 3 (*A*) Computed tomography contrast scan showing a heterogeneous mass of 6.1 × 5.3 cm in close proximity with the pulmonary arteries, the aorta, and the left atrium, with mass effect. Imaging characteristics were consistent with a mediastinal paraganglioma. (*B*) Follow-up computed tomography contrast scan (11 months after embolization): confirmed the successful embolization of the left circumflex coronary anomalous feeder branch and a slight decrease in tumour size from the initial to 61 × 53 × 33 mm to 59 × 50 × 29 mm.

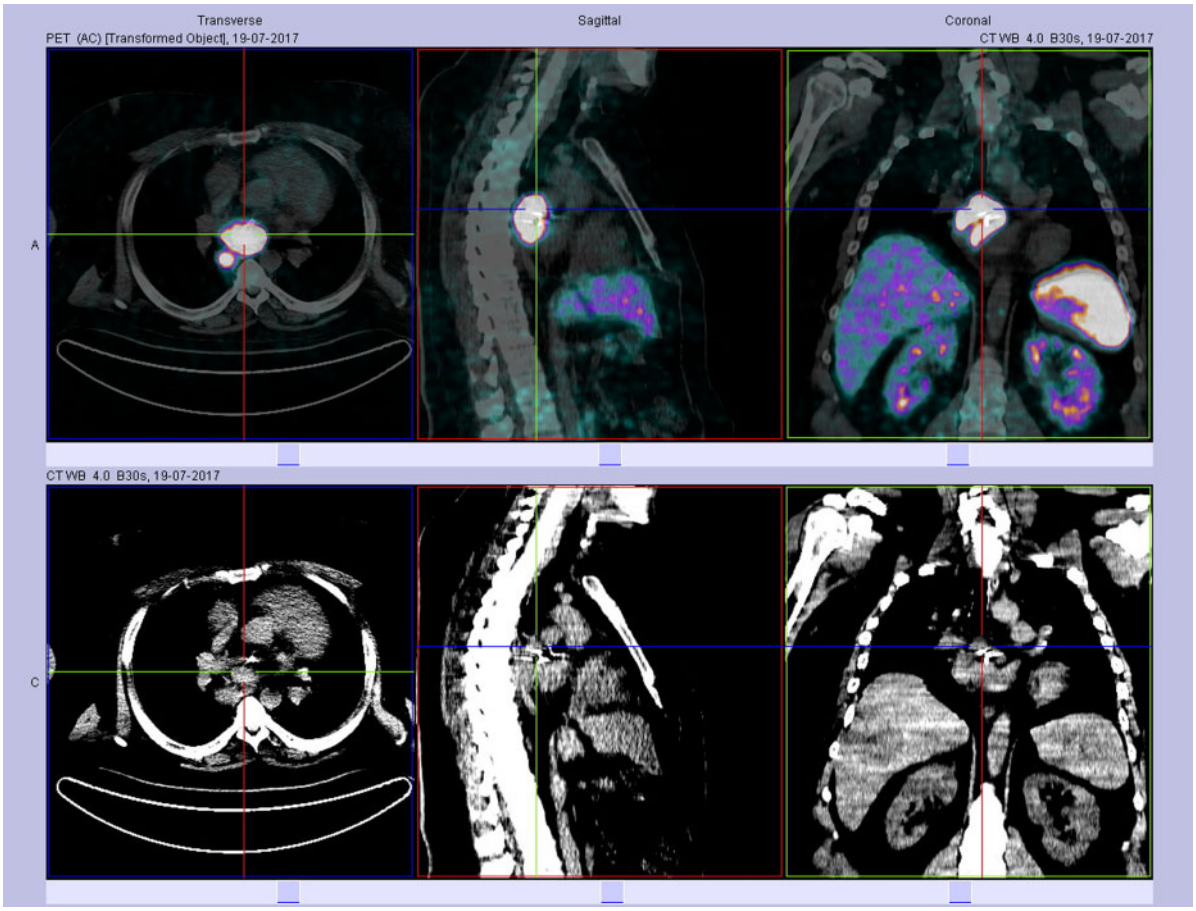


Figure 4 68-Galium-DOTANOC positron emission tomography scan confirming isolated mediastinal uptake and high expression of somastostatin receptors.

Discussion

Paragangliomaʼs located within the mediastinum are exceptionally rare, accounting for <2% of cases, and the majority being non-functional tumours.[1,2] According to the World Health Organization, PGs are not classified as benign or malignant but rather they represent a spectrum of metastatic potential. Patients with larger tumours, extra-adrenal locations and SDHB mutations are at higher malignancy risk.[4] Genetic testing is mandatory in all PG cases since mutations are found in the majority of pheochromocytoma and PG patients with family history but also in at least one-third of patients with sporadic tumours.[4] Establishing a hereditary syndrome is crucial for the earlier diagnosis of patients' relatives.

Paragangliomaʼs pose diagnostic and therapeutic challenges. Clinical presentation may be related to compressive effects or to catecholamine secretion.[2,3] With typical imaging results and according to functional studies, tissue diagnosis should be avoided due to the risk of bleeding and of catecholamine surges (acute release of catecholamineʼs into the bloodstream causing sudden severe hypertension and tachycardia).[4–6]

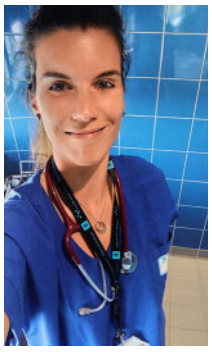
Alpha and beta blockade therapy prior to tumour manipulation minimizes the risk of surges.[2,6,7] Guidelines recommend complete surgical resection in non-metastatic PGs.[4,5] However, high rates of significant perioperative bleeding and even death have been observed in tumours with close proximity to the heart and major vessels.[1,8] Embolization strategies to minimize blood loss during resection were studied in head and neck PGs[9,10] but are only recently starting to be applied in mediastinal PGs with few case reports available.[11–13] In this case, embolization of the main feeder branch intended to reduce tumour vascularization and the risk of perioperative bleeding.

Peptide-receptor radionuclide therapy for neuroendocrine tumours with expression of somatostatin receptors has growing evidence of safety and efficacy.[14,15] Higher expression of somatostatin receptors correlates with better responses; in few cases complete remission was achieved.[15] Given the rarity of PGs experience is limited. Response to therapy is variable and might be delayed. Therefore, caution is advised in interpreting early follow-up CT scans. In this case, the goal with radionuclide therapy was to decrease tumour size and hormonal production to provide the best possible conditions for surgery. Even though surgery did not occur, the early controls performed showed positive signs (no metastasis, slight size reduction and successful embolization). By decreasing tumour-related surgical risk, these strategies offer promising results for suitable PG tumours initially considered inoperable or for patients at very high surgical risk.

Schizophrenia correlates with higher risk of cardiovascular disease, related to lower treatment of cardiovascular risk factors and to antipsychotic drug use that increases arrhythmia risk.[16] In this case, the mechanism of death (suicide) was unrelated to arrhythmia or coronary disease. However, chronically elevated catecholamineʼs levels can cause mood swings and might have contributed to aggravate the symptoms of schizophrenia. The stress from having a severe diagnosis in a mentally fragile patient added to high circulating catecholamineʼs levels probably played a role in this unfortunate outcome. Clinicians need to be vigilant to identify patients potentially at risk.

This case describes a very rare tumour with an unusual coronary supply. Our innovative strategies, combining coronary artery embolization with radionuclide therapy, were effective in decreasing tumour vascularization, size, and hormonal production. This is a promising approach for suitable PG tumours among patients at very high surgical risk.

Lead author biography



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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: Patient's next of kin (father) provided verbal and written consent for the publication of this case report.

Conflict of interest: none declared.

References

1. Brown ML, Zayas GE, Abel MD, Young WF, Schaff HV. Mediastinal paragangliomas: the mayo clinic experience. *Ann Thorac Surg* 2008;**86**:946–951.
2. Buchanan SN, Radecki KM, Chambers LW. Mediastinal paraganglioma. *Ann Thorac Surg* 2017;**103**:e413–e414.
3. Benn D, Robinson D, Clifton-Bligh R. 15 years of paraganglioma: clinical manifestations of paraganglioma syndromes types 1-5. *Endocr Relat Cancer* 2015;**22**: T91–T103.
4. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M, Pentheroudakis G; ESMO Guidelines Working Group. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;**23**(Suppl 7):vii131–vii138.
5. Lenders JWM, Duh Q-Y, Eisenhofer G, Gimenez-Roqueplo A-P, Grebe SKG, Murad MH, Naruse M, Pacak K, Young WF. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;**99**:1915–1942.
6. Vanderveen KA, Thompson SM, Callstrom MR, Young WF, Grant CS, Farley DR, Richards ML, Thompson GB. Biopsy of pheochromocytomas and paragangliomas: potential for disaster. *Surgery* 2009;**146**:1158–1166.
7. Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. *Clin Chem* 2014;**60**:1486–1499.
8. Ramlawi B, David EA, Kim MP, Garcia-Morales LJ, Blackmon SH, Rice DC, Vaporciyan AA, Reardon MJ. Contemporary surgical management of cardiac paragangliomas. *Ann Thorac Surg* 2012;**93**:1972–1976.
9. Michelozzi C, Januel AC, Cuvinciuc V, Tall P, Bonneville F, Fraysse B, Deguine O, Serrano E, Cognard C. Arterial embolization with Onyx of head and neck paragangliomas. *J NeuroIntervent Surg* 2016;**8**:626–635.

10. Ozyer U, Harman A, Yildirim E, Aytekin C, Akay TH, Boyvat F. Devascularization of head and neck paragangliomas by direct percutaneous embolization. *Cardiovasc Intervent Radiol* 2010;**33**:967–975.
11. Shakir M, Blossom G, Lippert J. Anterior mediastinal paraganglioma: a case for preoperative embolization. *World J Surg Oncol* 2012;**10**:134.
12. Brichon PY, Chavanon O, Thony F, Wion N. An intrapericardial paraganglioma with embolization of a large vessel from the left coronary artery. *Eur J Cardiothorac Surg* 2014;**45**:e234–e234.
13. González-Ferreiro R, Rodriguez-Ruiz E, López-Otero D, Martínez Monzonís A, Álvarez Barredo M, Trillo-Nouche R, González Juanatey JR. Percutaneous coronary intervention for treatment of paraganglioma with coronary vascularization. *JACC Cardiovasc Interv* 2017;**10**:958–960.
14. Chang CA, Pattison DA, Tothill RW, Kong G, Akhurst TJ, Hicks RJ, Hofman MS. (68)Ga-DOTATATE and (18)F-FDG PET/CT in Paraganglioma and Pheochromocytoma: utility, patterns and heterogeneity. *Cancer Imaging* 2016; **16**:22.
15. Hörsch D, Ezziddin S, Haug A, Gratz KF, Dunkelmann S, Miederer M, Schreckenberger M, Krause BJ, Bengel FM, Bartenstein P, Biersack H-J, Pöpperl G, Baum RP. Effectiveness and side-effects of peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: a multi-institutional registry study with prospective follow-up. *Eur J Cancer* 2016;**58**:41–51.
16. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease—a non-systematic review of epidemiology, possible causes, and interventions. *Front Psychiatry* 2014;**5**:137.