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CASE REPORT
Cardiac imaging

Added-value of molecular imaging in myocardial metastasis of an ileal neuroendocrine tumour treated with peptide receptor radionuclide therapy: a case report

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Background Neuroendocrine tumours (NET) conform a rare type of neoplasm, mostly located in the gastrointestinal tract. They are slow-growing tumours, so at the time of the diagnosis, most patients present with metastatic lesions, mainly in the liver. The myocardium is a rare and important organ for metastasis, in which ^{68}Ga-Dotatate positron emission tomography-computed tomography (PET/CT) shows a high diagnostic sensitivity for its detection, contrary to carcinoid valve disease, where anatomic imaging plays a key role, especially the echocardiogram.

Case summary A 60-year-old man diagnosed with metastatic progressive ileal NET, who underwent a ^{68}Ga-Dotatate PET/CT prior ^{177}Lu-Dotatate therapy, showed a metastatic lesion in the left ventricle that was undetected in previous studies, such as an Octreoscan® and CT. A transthoracic echocardiogram was performed revealing the existence of a second cardiac lesion, a tricuspid valve carcinoid disease. A cardiac magnetic resonance showed no late gadolinium enhancement.

Discussion The ^{68}Ga-Dotatate PET/CT is currently considered the gold standard for assessment and follow-up of NET, including those with rare sites of metastasis such as cardiac infiltration. In this case, it stimulated the persue of possible cardiac involvement, detecting the coexistence of two types of lesions (cardiac metastasis and carcinoid valve disease). Of these, carcinoid valvulopathy develops in 50% of NET cases, while cardiac metastasis (CM) is less frequent (only 5%).

Keywords NET • PRRT • Cardiac metastasis • Carcinoid valvulopathy • ^{68}Ga-DotatatePET/TC • Case report

Learning points

- The heart is an unusual area of metastatic disease in neuroendocrine tumours (NET) and is commonly asymptomatic.
- ^{68}Ga-Dotatoc positron emission tomography-computed tomography (PET/CT) is the gold standard for the initial diagnosis and follow-up of NET, being superior to Octreoscan.
- ^{68}Ga-Dotatoc PET/CT appeared to be superior to Octreoscan, CT, and cardiac magnetic resonance in the detection of cardiac metastasis.

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Introduction

Neuroendocrine tumours (NET) are a rare type of neoplasms, mainly located in the gastrointestinal tract. They are slow-growing tumours, causing little or no symptoms at the onset of the disease, which explains why at the time of diagnosis most patients present metastatic lesions,[1] predominantly in the liver, followed by the bone, lung, and peritoneum.[2]

The myocardium is a rare location for carcinoid metastasis. Carcinoid heart disease is usually asymptomatic and can affect any of the cardiac chambers, the interventricular septum, or the pericardium,[3] and can go unnoticed in a significant percentage of cases.

One of the main characteristics of NET is a high density of somatostatin receptors (SSTR) on their cell surface, primarily type 2 (SSTR2),[2] which function as a target for somatostatin analogs used both in molecular imaging techniques and in radionuclide-directed therapy.

Molecular imaging techniques, like somatostatin receptor scintigraphy (Octreoscan®) and positron emission tomography with ^{68}Ga-Dotatoc [^{68}Ga-Dotatoc positron emission tomography-computed tomography (PET/CT)], facilitate the diagnosis of the primary tumour and metastatic lesions in their most frequent locations. However, ^{68}Ga-Dotatoc PET/CT has higher diagnostic sensitivity by quickly detecting unsuspected and small size lesions such as myocardial infiltration (1, 2, and 3).

On the other hand, carcinoid valvulopathy (CV) is a significant cause of morbidity and mortality in patients with metastatic NET.[3] Contrary to what happens with cardiac metastases (CM), functional imaging is not essential in the diagnosis of CV for it is not based on the expression of SSTR, but on the release of vasoactive substances by the tumour as a result of chronic exposure to excessive levels of circulating serotonin, which generate fibrous plaques that are deposited on the heart valves.[1,3] These types of lesions frequently appear in small intestine NET cases, mainly affecting the right-sided chambers, which can be assessed in an echocardiogram, revealing possible progressive valvular dysfunction.[1]

The case of a patient diagnosed with ileal NET and associated double cardiac injury (CM and CV) is reported below. Verbal and written consent was signed by the patient.

Case presentation

A 60-year-old hispanic man was referred for peptide receptor radionuclide therapy (PRRT) for a progressive metastatic ileal neuroendocrine tumour (NET). The patient was initially diagnosed through routine scanning and treated with several lines of treatments from 2003 to 2018 which included a right hemicolectomy, hepatic arterial embolization, long-lasting octreotide, and the resection of two peritoneal implants. Afterward, the patient received treatment with pegylated interferon, and due to new progression, everolimus and octreotide were added. The patient later presented with new hepatic and peritoneal disease, and ^{177}Lu-Dotatate treatment was started after being discussed in the endocrine tumour board.

Treatment with PRRT was approved after confirming somatostatin receptor-positive lesions in the liver, segments III, IV, and VIII. The administration of the first dose of PRRT was delayed until October 2018, due to intestinal obstruction requiring jejunal loop resection and jejunal-ileal anastomosis; this intervention confirmed the existence of peritoneal carcinomatosis with a Ki-67 of 5%.

Once recovered from surgery, a ^{68}Ga-Dotatoc PET/CT was performed to rule out other possible foci of metastatic disease, which confirmed not only multifocal hepatic tumour infiltration and peritoneal carcinomatosis but also identified a cardiac lesion in the left ventricle that expressed a high density of SSTR, compatible with CM (*Figure 1*). This cardiac lesion was not visualized in previous Octreoscan® nor a tomographic study (CT). In physical examination, the patient was normotensive (122/84 mmHg), with 67 beats/minute, had prominent jugular veins with a prominent 'v wave' alongside the Kussmaul's sign. A holosystolic murmur was heard at the left mid sternal border, with no palpable thrill, followed by a strong second heart sound.

Given recent findings, a transthoracic echocardiogram was requested to assess cardiac involvement, with an incidental diagnosis of tricuspid valve disease, characterized by a retraction and thickening of the leaflets with decreased mobility, suggesting CV, and severe tricuspid regurgitation (*Video 1*: transthoracic echocardiogram study, 2D study of four-chamber apical view; *Video 2*: transthoracic echocardiogram study, 2D view of tricuspid regurgitation in parasternal modified view; *Video 3*: transthoracic echocardiogram study). Colour Doppler of tricuspid regurgitation in parasternal

Timeline

2003–2018	Diagnosis of ileal neuroendocrine tumour (NET) and treatment with several lines: • Surgical intervention • Sandostatin. • Hepatic radioembolization. • Resection of two peritoneal implants. • Systemic therapy with Pegylated interferon + Everolimus + Octreotide
June 2018	Disease progression (liver and peritoneal).
03 October 2018	^{68}Ga-Dotatoc positron emission tomography-computed tomography to rule out other possible foci of metastatic disease. A cardiac lesion in the left ventricle was identified with a high density of somatostatin receptors expression.
17 October 2018	Echocardiogram suggesting carcinoid valvulopathy. Cardiac magnetic resonance showed no late gadolinium enhancement.
30 October 2018–28 May 2019	^{177}Lu-Dotatate treatment.
Present	Follow-up. Currently asymptomatic with stable disease.

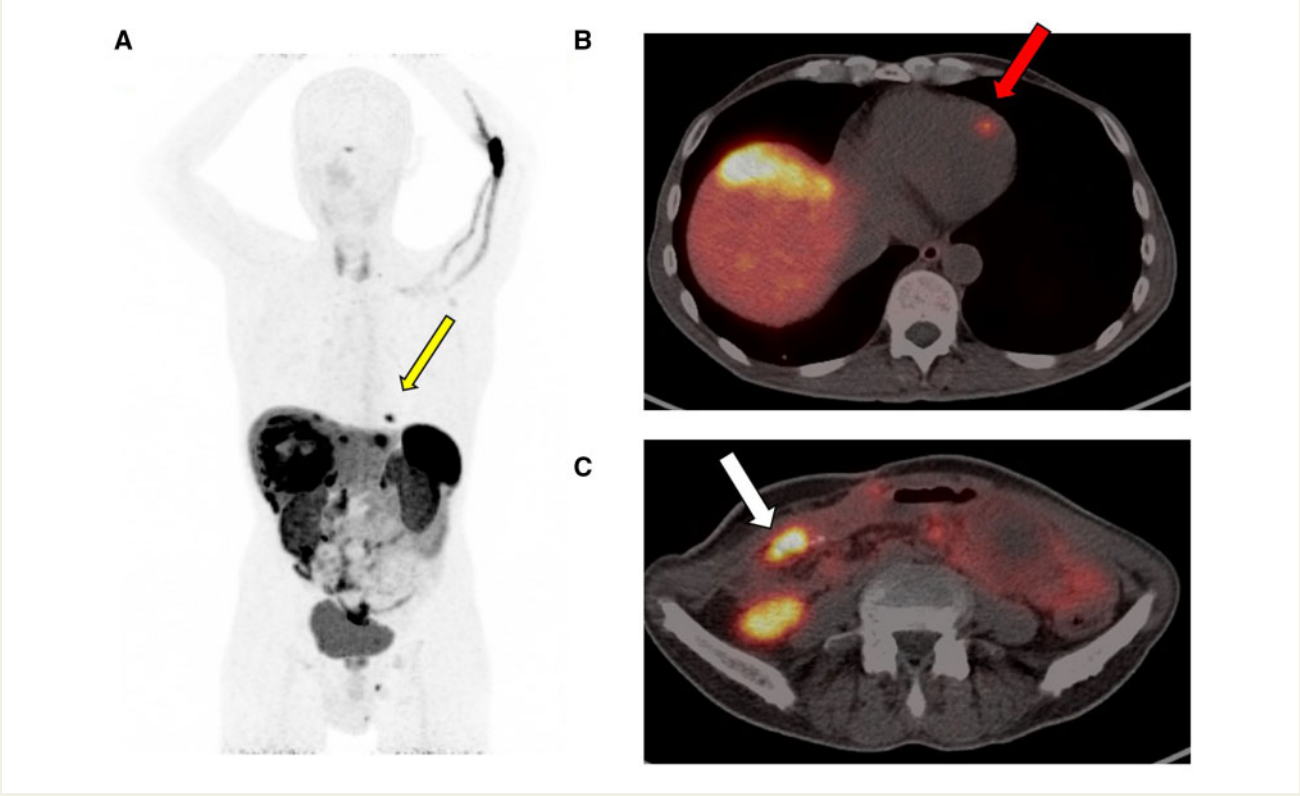
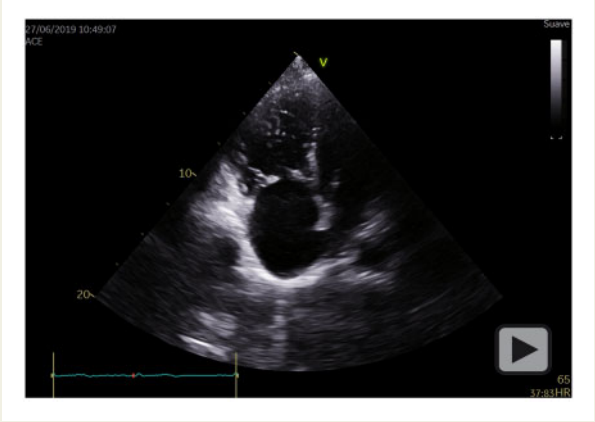
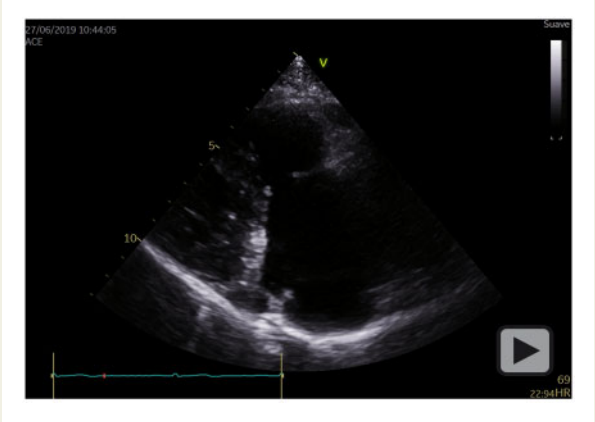


Figure 1 ^{68}Ga-Dotatoc positron emission tomography-computed tomography. Whole-body maximum intensity projection positron emission tomography shows high radiotracer uptake in the myocardium (*A*; yellow arrowhead) and a fused positron emission tomography-computed tomography in the cardiac area (*B*; red arrowhead) and tumour in the terminal ileum (*C*, white arrowheads).



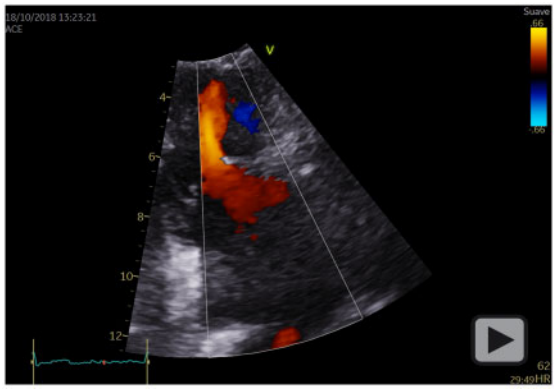
Video 1 Transthoracic echocardiogram study. 2D view of four chamber apical view. Retraction and thickening of the leaflets with decreased mobility is observed.



Video 2 Transthoracic echocardiogram study. 2D view of tricuspid regurgitation in parasternal modified view.

modified view. Based on these results, the coexistence of two types of cardiac lesions was confirmed in an asymptomatic patient from a cardiovascular point of view. A cardiac magnetic resonance was performed and no late gadolinium enhancement was found in the left ventricle (*Figure 2*).

The patient received the first dose of PRRT on 30 October 2018, after which he presented with two further episodes of intestinal obstruction; the first at the end of December 2018, treated with a jejunum-colic bypass, and the second in January 2019 treated conservatively. The second dose was administered on 1 January 2019, with a CT study performed on 13 March 2019 demonstrating stable disease.



Video 3 Transthoracic echocardiogram study. Colour Doppler showing severe tricuspid regurgitation in parasternal modified view. Vena contracta width of 11 mm.

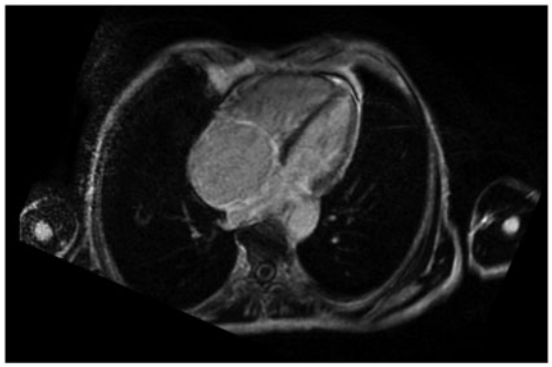


Figure 2 Cardiac magnetic resonance: no late gadolinium enhancement was found in the left ventricle.

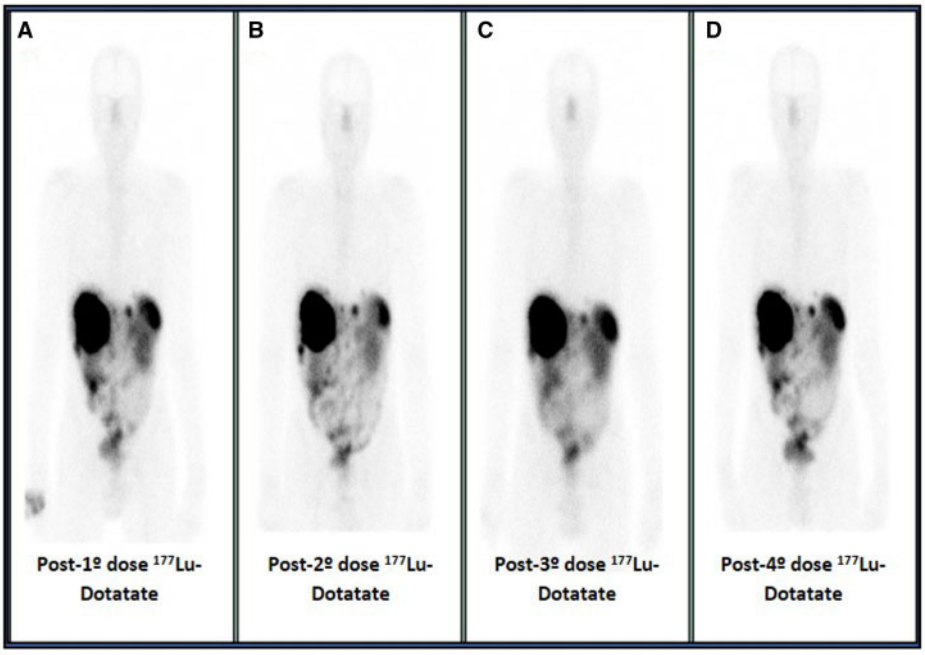


Figure 3 Scintigraphic evaluation after the administration of each therapeutic dosage of PRRT: the uptake of the therapeutic dose was confirmed in the known lesions (liver, ileum, and myocardium), after the administration of each therapeutic dosage of ^{177}Lu-Dotatate, first (*A*), second (*B*), third (*C*), and fourth (*D*).

The patient completed the treatment with the administration of two more doses (26 March 2019 and 28 May 2019) of PRRT without complications; a new ^{68}Ga-Dotatoc PET/CT was carried out, showing a partial hepatic and peritoneal response with the stability of the rest of the lesions.

After the administration of each dose of PRRT, a whole-body scintigraphy was performed (*Figures 3* and *4*), confirming an uptake in the existing lesions, as well as the cardiac metastasis. During follow-up, this patient remained asymptomatic with a progression-free survival of 22.4 months to date.

Discussion

Somatostatin receptor scintigraphy is one of the routine functional tests performed in the diagnosis of patients with NET; however, in

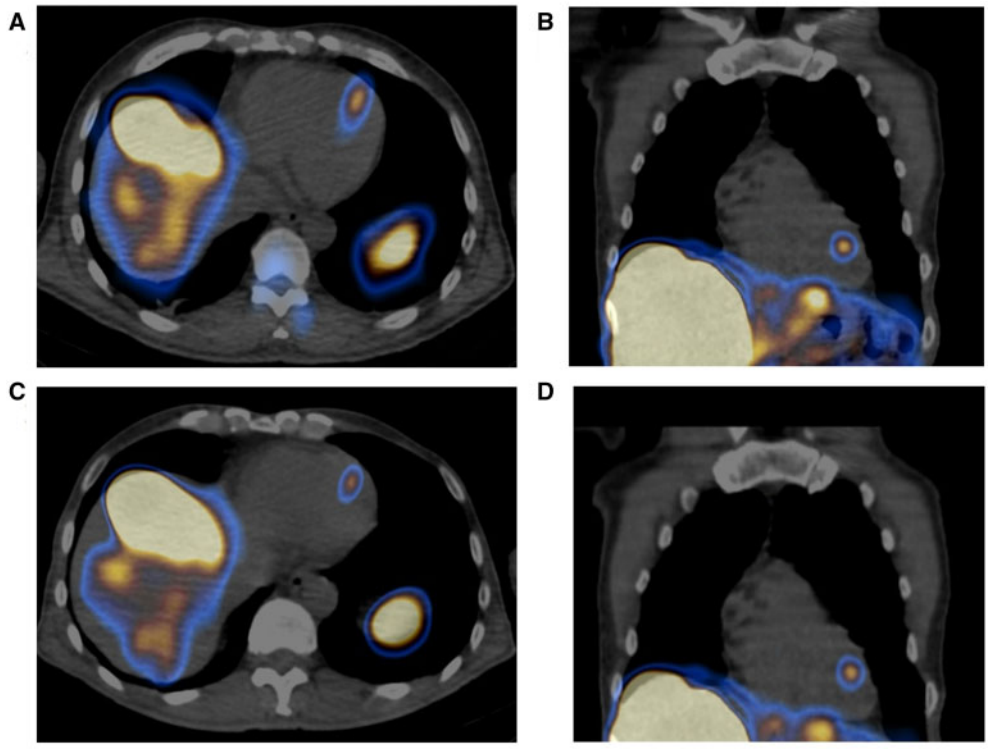


Figure 4 Single-photon emission - Computed tomography (SPECT/CT) images after administration of the first (*A* and *B*) and the fourth (*C* and *D*) dose of ^{177}Lu-Dotatate.

this case, it was not until a ^{68}Ga-Dotatoc PET/CT was performed that a myocardial lesion in the left ventricle was discovered, using a technique with higher sensitivity for this type of pathology. Srirajakanthan *et al.* demonstrated that ^{68}Ga-Dotatoc could identify lesions in patients with NET with negative findings in Octreoscan® due to its higher avidity for type 2 SSTR.[2]

Therefore, ^{68}Ga-Dotatoc PET/CT had been accepted as the current gold standard for initial diagnosis and follow-up of patients with well-differentiated NET.[3] It has been established that this type of test makes it easier to carry out a definitive diagnosis and staging of NET in a non-invasive way.[4]

In this patient, the existence of a second carcinoid lesion in the heart was discovered after cardiac evaluation. The typical echocardiographic appearance of tricuspid valvulopathy consists of leaflet retraction, thickening, and reduced mobility. This represents an independent prognostic factor in patients with advanced disease.[1] While CV develops in 50% of the patients with NET with carcinoid syndrome, cardiac metastases are much rarer and have been recorded in less than 5% of the population.[3] Calissendorff *et al.* reported four patients with ileal NET and cardiac metastases detected by ^{68}Ga-Dotatoc PET/CT in a study whose incidence of cardiac metastases was 4.3%.[2]

Regarding cardiovascular symptoms, cardiac metastases appear to be clinically asymptomatic whereas valvular disease may cause heart failure symptoms,[1,2] hence the importance of thorough cardiac monitoring in these patients.

Conclusions

Molecular imaging techniques are useful in the initial diagnosis and extension of NET, highlighting the use of ^{68}Ga-Dotatoc PET/CT, which due to its high sensitivity, could increase the detection of lesions in unusual areas such as the heart.

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: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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