**Case Report**

# Carcinoid Heart Disease and a Complicated Course of Progressive Gastroenteropancreatic Neuroendocrine Neoplasia: A Case Report

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**Abstract**

***Introduction:*** Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are a relatively rare, heterogenous group of malignancies originating from secretory cells of the neuroendocrine system. Carcinoid syndrome is a complication of neuroendocrine tumours, characterized by a triad of flushing, bronchospasm, and diarrhoea. This is due to the release of serotonin and other vasoactive substances by the tumour. Elevated levels of serotonin can also cause fibrotic changes in the structures of the heart, which can lead to cardiac complications termed carcinoid heart disease. We report the case of a 64-year-old man diagnosed with carcinoid heart disease 19 years after his initial diagnosis of grade 2 GEP-NET with liver metastases. ***Case Presentation:*** The patient presented with symptoms of shortness of breath, lower limb swelling, abdominal swelling, and chest pain. He was on treatment with subcutaneous lanreotide 120 mg twice weekly prior to admission. An echocardiogram showed moderate tricuspid regurgitation and mitral regurgitation but preserved left ventricular systolic function, consistent with right heart failure. A CT pulmonary angiogram showed a small volume left lingula pulmonary embolism with bilateral pleural effusions and stable pericardial effusion with evidence of right ventricular strain. The patient was started on IV furosemide 40 mg twice daily, SC octreotide 100 µg three times daily, and therapeutic tinzaparin. The patient was discharged following successful diuresis. ***Conclusion:*** This case report highlights the importance of regular echocardiogram and cardiovascular checkups in patients with carcinoid tumours and liver metastases. A multidisciplinary approach involving medical oncologists, cardiothoracic surgeons, and cardiologists is vital in ensuring early treatment and preventing late-stage complications of carcinoid heart disease.

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## Introduction

Gastroenteropancreatic neuroendocrine tumours are relatively rare tumours with origins from neurosecretory cells [1]. They are classified by anatomical origins (foregut, midgut, or hindgut), degree of differentiation, proliferation index, and whether they are functional or not (hormone secreting). Well-differentiated neuroendocrine tumours are further graded based on Ki67 index, which is a measure of tumour cell proliferation and growth, and mitotic count. They are classified as follows: (1) NET grade 1: less than 2 mitoses/10HPF, Ki67 index of less than 3. (2) NET grade 2: 2 to 20 mitoses/10HPF, Ki67 index 3 to 20. (3) NET grade 3: more than 20 mitoses/10HPF, Ki67 index of more than 20. Poorly differentiated neoplasms are called neuroendocrine carcinomas, which can be divided into small-cell or large-cell carcinomas [2]. Patients with neuroendocrine tumours can present with carcinoid syndrome. Carcinoid syndrome is characterized by a triad of facial flushing, bronchospasm, and diarrhoea. The incidence of carcinoid syndrome among patients with neuroendocrine tumours is approximately 50%, of whom about 50% develop carcinoid heart disease [1]. Carcinoid heart disease, characterized by right-sided heart valve fibrosis, is caused by the release of vasoactive substances such as serotonin, histamine, tachykinins, and prostaglandins by the tumour cells. These substances are usually inactivated by the liver, lungs, and brain. However, in the case of liver metastases, large amounts of these vasoactive substances reach the right side of the heart without being inactivated by the liver. Consequently, endocardial plaques of fibrous tissue get deposited onto the valves causing distortion that leads to stenosis, regurgitation, or both [1, 3]. Only about 15% of patients have left-sided valve involvement due to the inactivation of the vasoactive substances in the lungs [4]. Left-sided valve involvement could be due to extensive liver metastases, bronchial carcinoid, or a patent foramen ovale [1]. In most cases, the tricuspid valve is affected, with or without pulmonary valve involvement [4]. Here we describe the case of a 64-year-old gentleman who presented with symptoms of right heart failure and chest pain 19 years after his initial diagnosis of grade 2 neuroendocrine tumour with liver metastases originating in the gastrointestinal tract.

## Case Presentation

We present the case of a 64-year-old single male patient with a past medical history of schizoaffective disorder, diagnosed with a grade 2 neuroendocrine tumour with liver metastases in 2004 following a right hemicolectomy. Following this, the patient was started on lanreotide 30 mg every 2 weeks. Unfortunately, the patient declined follow-up appointments by the medical oncology team until 2015 but remained on lanreotide. The patient also declined repeat imaging until May 2019.

In May 2019, the patient attended the hospital due to bulging of the right eye, first noticed by the patient's general practitioner. MRI of the orbits and CT of the brain failed to identify any abnormality. Thyroid function test was normal. However, a CT of the thorax, abdomen, and pelvis revealed progression of disease with enlarged mesenteric, pelvic, and peritoneal soft tissue masses, increased hepatic metastatic disease, and metastatic lymphadenopathy compared to previous examination in 2005. Serum chromogranin A was 881. The patient's lanreotide was increased to 60 mg every 2 weeks.

In May 2020, a repeat CT of the thorax, abdomen, and pelvis showed stable disease and new borderline cardiomegaly. An echocardiogram was performed, which showed mild to moderate tricuspid regurgitation, mildly dilated right atrium but no evidence of mitral regurgitation or stenosis. Left ventricular ejection fraction was more than 55%. Serum

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chromogranin A was 1,567. Following the rising trend of serum chromogranin A, chemotherapy was offered but declined by the patient. Lanreotide was increased to 120 mg every 2 weeks.

In September 2020, a CT of the thorax, abdomen, and pelvis showed stable disease, with an interval development of a small pericardial effusion. His BNP was 104. Following this, the patient was regularly followed up every 6 months with serum chromogranin A and three-monthly CT.

Serum chromogranin A in February 2022 showed a decrease, at 1,260. The patient subsequently refused an Octreoscan. He remained on lanreotide 120 mg every 2 weeks. He was regularly followed up every 4 months, with no reported symptoms of breathlessness in each visit.

In September 2023, the patient presented to the hospital with chest pain, shortness of breath, abdominal swelling, and bilateral leg swelling. On physical examination, the patient appeared flushed, with bilateral proptosis, worse on the right side (Fig. 1). Bibasal crackles were present on auscultation of the lungs. A pansystolic murmur was evident on auscultation of the heart. The liver was palpable 8 cm below the right costal margin, with pedal oedema up to the knees (Fig. 2, 3).

An electrocardiogram performed revealed a new-onset atrial fibrillation. CT pulmonary angiogram was performed following a high initial D-dimer. This revealed a small volume left lingula pulmonary embolus with bilateral pleural effusions, worse on the right. The pericardial effusion was stable, with evidence of right heart strain in the form of intrahepatic reflux of contrast. A CT of the abdomen and pelvis were done to assess metastatic burden. This showed overall increased metastatic disease burden in the liver, with interval enlargement of multiple epicardial lymph nodes. Moderate volume ascites and peritoneal nodularity were identified, in keeping with peritoneal carcinomatosis. His BNP was 2620 on admission. A 24-h urinary 5-HIAA was sent and eventually came back after patient's discharge at 1,571.

Due to the worsening proptosis, an MRI of orbits was requested, which showed a lobulated hypoenhancing mass within the belly of the right lateral rectus muscle suspicious for malignancy. Both lateral rectus muscles appeared slightly thickened.

An echocardiogram was performed, which revealed an overall preserved left ventricular systolic function. Both atria were enlarged, with mildly enlarged right ventricle. There was moderate tricuspid and mitral regurgitation, with mild to moderate aortic insufficiency (Fig. 4, 5). The working diagnosis was exacerbation of right heart failure secondary to carcinoid heart disease, with complicating left lingula pulmonary embolus and new-onset atrial fibrillation.

The patient was started on IV furosemide 40 mg twice daily, with SC Octreotide 100 µg three times daily. Therapeutic-dose tinzaparin was commenced for the pulmonary embolism. The patient's weight, renal function, and BNP were monitored to assess fluid status. Treatment was well tolerated with improvement to symptoms, mainly shortness of breath. The patient was discharged following successful diuresis with follow-up in the medical oncology clinic.

## Discussion

Neuroendocrine tumours are rare tumours that often arise in the gastrointestinal tract. While they are slow-growing tumours, half of patients with neuroendocrine tumours will eventually develop carcinoid syndrome, characterized by a triad of flushing, diarrhoea, and bronchospasm. As many as half of patients with carcinoid syndrome will develop carcinoid heart disease. The time between emergence of these symptoms and the diagnosis of carcinoid

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**Fig. 1.** Bilateral proptosis worse on the right side with facial flushing.
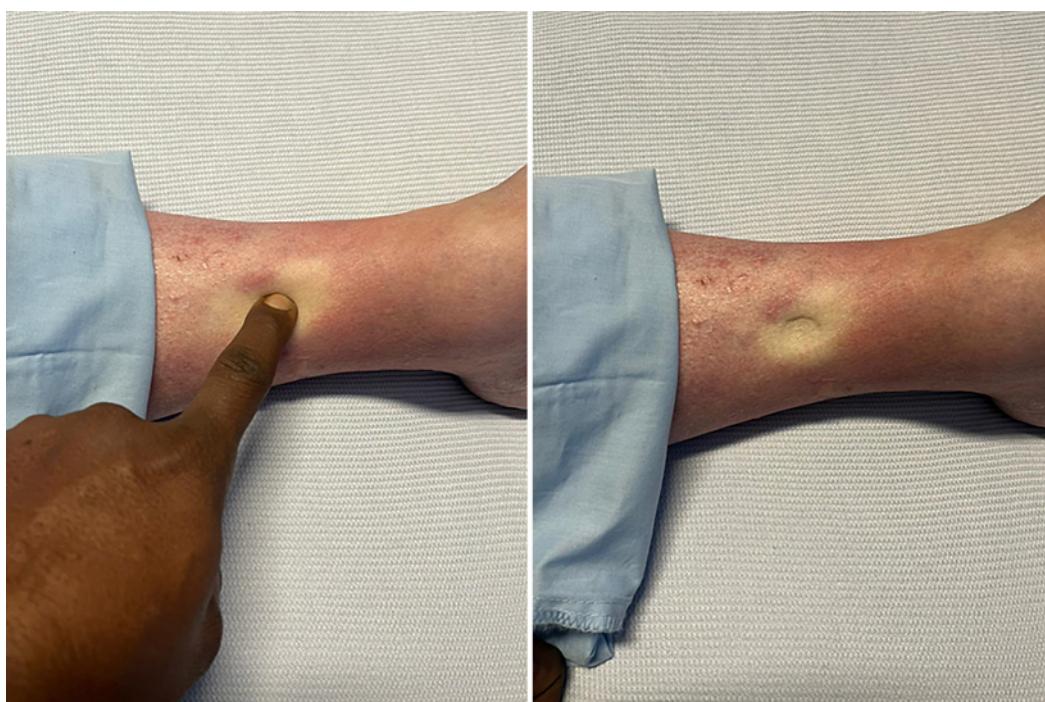


**Fig. 2.** Pitting oedema on application of pressure to lower limbs.

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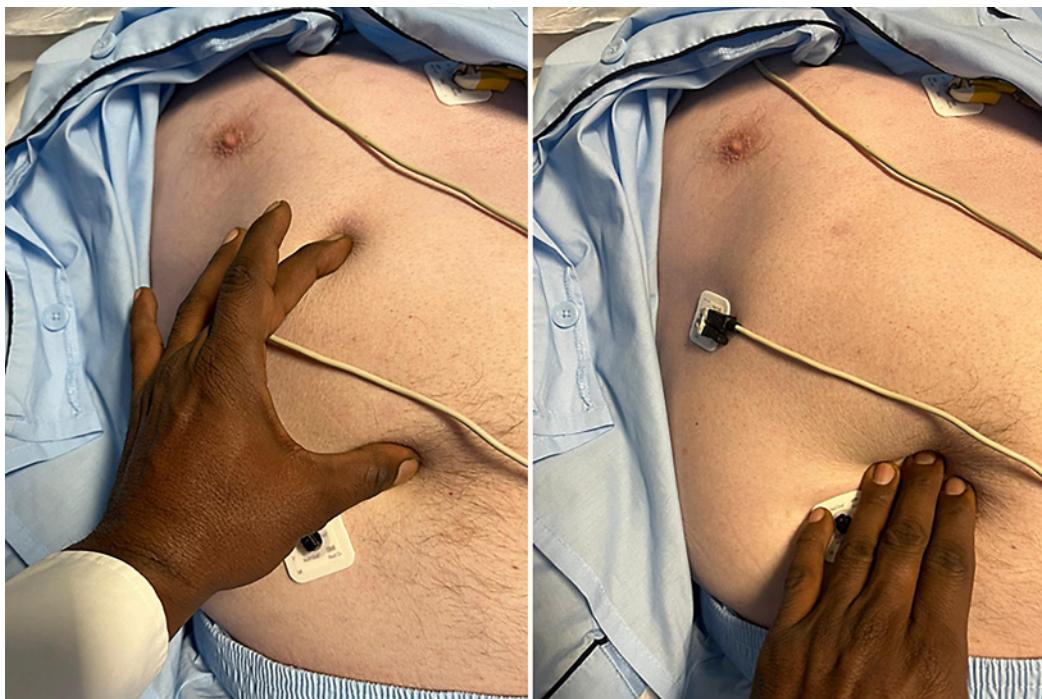
**Fig. 3.** Non-tender hepatomegaly identified on examination with liver edge palpable 8 cm below costal margin.

heart disease is estimated to be 24–28 months but can be as long as 5 years [5]. Despite its rarity, carcinoid heart disease carries a high mortality rate, with one study reporting reduced mean survival to 1.6 years in patients with carcinoid heart disease, compared to 4.6 years in those without cardiac involvement [6]. Our patient's history reflects this slow-growing process and the diagnostic challenges surrounding it, especially when many interventions and investigations were declined.

Carcinoid heart disease typically affects right-sided valvular structures due to the inactivation of vasoactive substances by the lungs before they reach the left side of the heart. It is estimated that left-sided valvular structures are involved in 5–10% of cases [1]. A large US-based case series revealed that 97% of 74 patients with carcinoid heart disease had tricuspid valve disease, with 90% of these displaying moderate or severe tricuspid regurgitation. Pulmonary valve involvement was noted in 88% of the patients. Left-sided involvement was present in 7% of patients [6]. Valve dysfunction is mainly due to presence of carcinoid plaques causing thickening of valve structures, caused by both cellular proliferation and extracellular matrix deposition [7]. In severe cases, the definitive treatment is valve replacement. Evidence exists to support increased quality of life among patients who were successfully treated with surgery [8]. However, mortality rate associated with valve surgery in these patients is high, with one clinical study reporting 35% perioperative deaths, mainly from postoperative bleeding and right ventricular failure [8].

In evaluating patients with neuroendocrine tumours, urine 5-HIAA level is a predictor of the development of carcinoid heart disease. One prospective study concluded that a urine 5-HIAA level of ≥300 μmol/24 h to 599 conferred 2.74 times the risk of progression of carcinoid heart disease [9]. Urine 5-HIAA is also a predictor of mortality in patients with neuroendocrine tumours. A systematic review and meta-analysis performed in 2019 revealed that for every 10-unit increase in urine 5-HIAA level, 12-month mortality incidence is increased by

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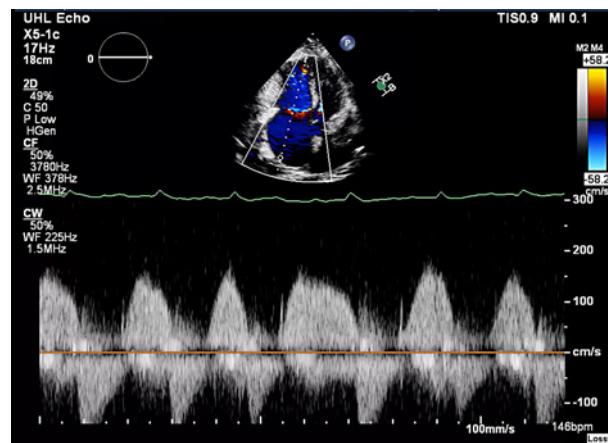
**Fig. 4.** Colour Doppler echocardiogram showing moderate tricuspid regurgitation and enlarged right ventricle and atrium.
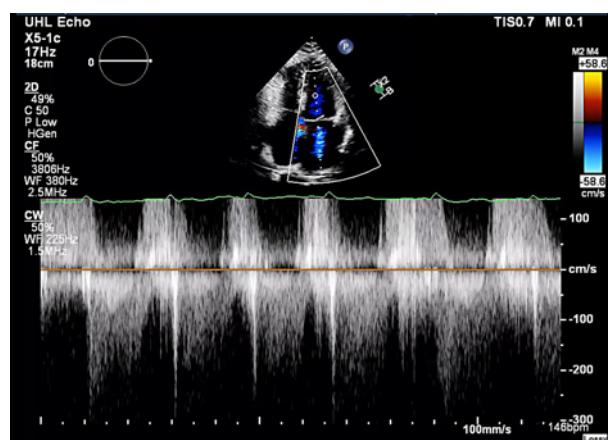


**Fig. 5.** Colour Doppler echocardiogram showing moderate mitral regurgitation and enlarged left atrium.

11.8% [10]. Apart from urine 5-HIAA measurement, NT-proBNP is a useful prognostic and diagnostic biomarker in carcinoid heart disease. A study found that the median NT-proBNP level was significantly higher in patients with carcinoid heart disease compared to patients with carcinoid syndrome without cardiac involvement. Subsequently, the authors concluded that a cutoff level of 260 pg/mL for detection of carcinoid heart disease is 92% sensitive and 91% specific, making it a good screening test [11].

In patients with established carcinoid heart syndrome, 6-monthly echocardiograms have been suggested, with cardiac MRI being advantageous in assessing change in size and function of the right ventricle [12]. While cardiac metastases from carcinoid tumour are extremely rare, echocardiograms and cardiac MRI are not able to differentiate between carcinoid metastases or another primary cardiac tumour [13]. In these cases, nuclear imaging technique such as $^{68}$Ga-DOTA-TOC PET is helpful in detecting cardiac metastases from a carcinoid tumour, with one study reporting a 97% sensitivity and 92% specificity for metastatic deposits in patients with neuroendocrine tumours [14].

Early referral for valve replacements should be considered in selected patients. Infusion of octreotide may be required peri- and post-operatively to reduce the risk of carcinoid crisis leading to hypotension during and after surgery [15]. While both mechanical and bioprosthetic valves have been used in right-sided valve replacements in carcinoid heart disease, recent reports favour the latter [15]. This is mainly due to the need for warfarin with mechanical valves. This is further disadvantaged by presence of liver

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metastases in patients with carcinoid disease, which confers a very high risk from bleeding [1].

In patients who are not fit for surgical treatment, the use of loop diuretics and digoxin is helpful in treating right heart failure, alongside careful fluid restriction. Thiazide diuretics may be added to achieve diuresis [1]. Furthermore, somatostatin analogues such as octreotide and lanreotide have been shown to improve survival in patients with carcinoid heart disease. However, none of these treatments have been shown to reverse the cardiac damage secondary to carcinoid disease [1].

Additionally, this case reveals an underlying need to establish a guideline in the patient selection criteria and timing of surgical intervention in carcinoid heart disease. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539257).

## Conclusion

We presented a case of a 64-year-old gentleman who presented with symptoms of right heart failure and chest pain 19 years after his initial diagnosis of grade 2 neuroendocrine tumour with liver metastases originating in the gastrointestinal tract. This case highlights the complexity of the management of neuroendocrine tumours and carcinoid heart syndrome. Early referral to cardiothoracic surgeons in view of valve replacements should be prioritized, and multidisciplinary management of such cases is important.

## Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent to publish the medical case and accompanying images was obtained from the patient and next of kin.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

F.A.M.N. wrote the manuscript with input from N.O. and S.O.S.

## Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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