

A clinical and echocardiographic case report of carcinoid-related valvular heart disease

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Background

Carcinoid syndrome is a rare disease caused by malignant neuroendocrine neoplasms. When vasoactive substances enter the systemic circulation, the triad of cutaneous flushing, bronchospasm, and diarrhoea often characterize carcinoid syndrome. Rarely, carcinoid syndrome can progress to involve the cardiac system, a condition known as carcinoid heart disease, often affecting right-sided valvular structures.

Case summary

Here, we present a case of malignant carcinoid syndrome with associated carcinoid heart disease in a 63-year-old female. The diagnosis of her dual regurgitant and stenotic valvular disease is detailed, with accompanying two- and three-dimensional echocardiographic images demonstrating the patient's complex tricuspid dysfunction.

Discussion

Carcinoid heart disease encompasses a rare but important subset of valvular dysfunction caused by circulating vasoactive substances. Diagnosis utilizing serum studies, computed tomography scans, and echocardiography can help expedite the diagnosis and treatment of such rare conditions, and assist in the avoidance of complications. Despite its relatively well-recognized clinical presentation, carcinoid syndrome and its associated heart disease still remains a challenging condition to manage and treat, often requiring the input of several subspecialties to treat the condition appropriately.

Keywords

Case report • Carcinoid heart disease • Tricuspid regurgitation • Neuroendocrine neoplasms

Learning points

- Carcinoid syndrome is a condition characterized by bronchospasm, flushing, and diarrhoea, that, in certain circumstances, can cause carcinoid heart disease.
- Often, the valvular and subvalvular effects of the syndrome can be attributed to extracellular matrix deposition, resulting in cardiac dysfunction.
- Management of carcinoid syndrome can be challenging, but often involves utilizing somatostatin analogues, such as octreotide, and the cardiac effects commonly being medically managed using loop or thiazide diuretics.
- The treatment of carcinoid heart disease can be complex, and formal guidelines for management are lacking; however, multidisciplinary management for the diagnosis and treatment of this rare syndrome is often necessary.

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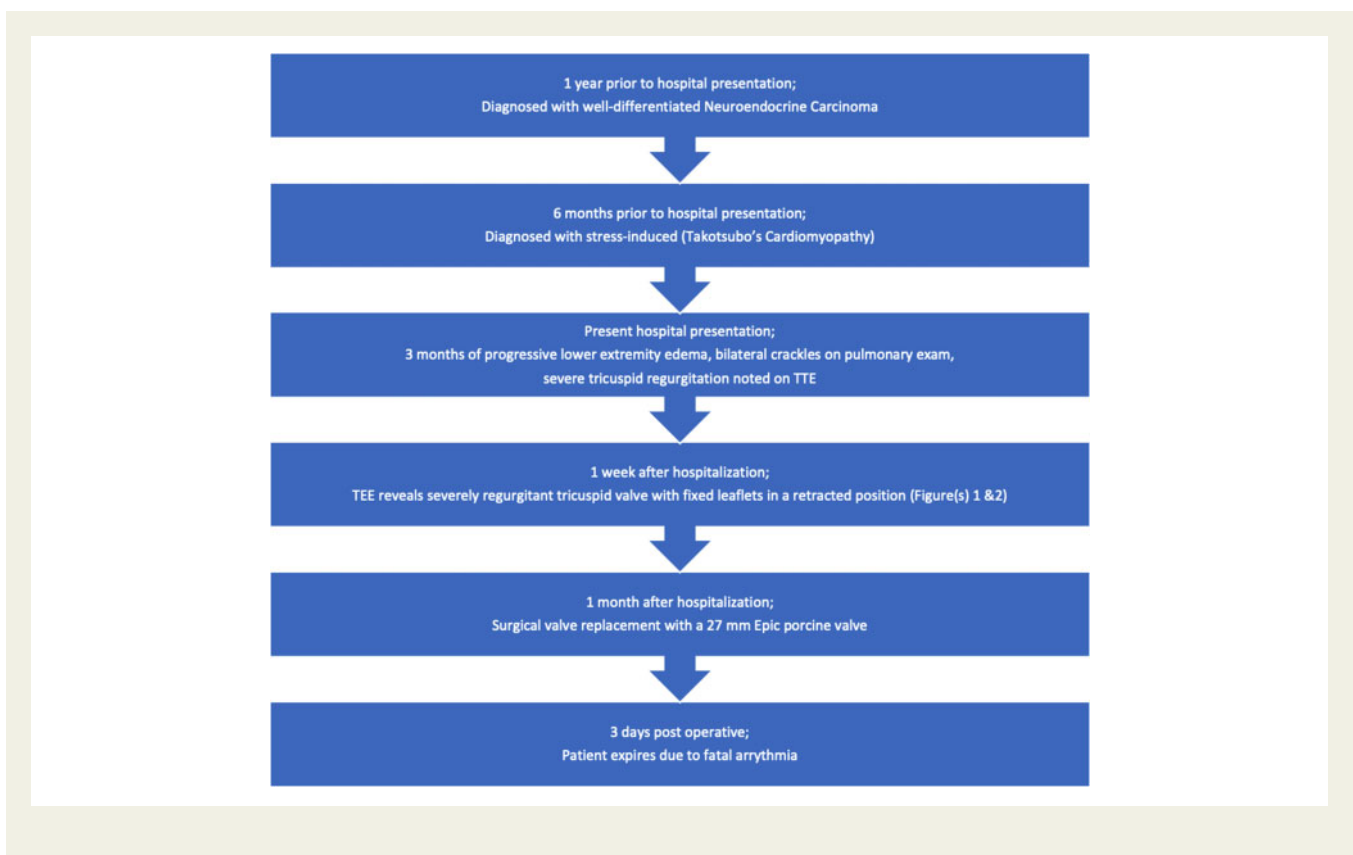
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Introduction

The carcinoid syndrome is a clinical condition defined by the symptomatic triad of bronchospasm, diarrhoea, and cutaneous flushing. The constellation of these symptoms can be ascribed to the circulation of vasoactive substances and their metabolites that can become deposited on or around intracardiac and valvular structures, contributing to the development of carcinoid heart disease. A rare cause of right-sided heart disease, only found in ~20% the patients diagnosed with carcinoid syndrome, carcinoid heart disease, often affects right-sided structures such as the tricuspid or pulmonic valve, often causing regurgitation or, more rarely, stenosis of right-sided structures.^{1,2} Identification and diagnosis of carcinoid heart disease is often with 2D or 3D echocardiographic evaluation.³ Here we present an echocardiographic case of carcinoid heart disease displaying the less commonly encountered behaviour of being both regurgitant and stenotic due to structural changes caused by circulating hormones.

was notable for basilar crackles bilaterally and a soft II/VI systolic murmur at the right mid sternal border accompanied by jugular venous distention. She was initially diagnosed with the neuroendocrine carcinoma 1 year previously. Six months previously, the patient presented to our hospital with complaints of chest pain that was ultimately diagnosed as stress-induced (Takotsubo's) cardiomyopathy. Repeat transthoracic echocardiography (TTE) during the present evaluation revealed a recovered left ventricular ejection fraction (LVEF) (55–60%) compared with previous studies but, unexpectedly, the patient now displayed severe tricuspid regurgitation. A transoesophageal echocardiogram (TEE) was performed 1 week later to further define her valvular anatomy, and demonstrated a severely regurgitant tricuspid valve with fixed leaflets in a retracted position (Figures 1 and 2). The valve leaflets, as well as the subvalvular apparatus including the chordae and papillary muscles, appeared markedly thickened (Figure 3). The affected valve appeared to be stented open, displaying both regurgitant and stenotic behaviour. Paralleling her diagnostic workup by the patient's internal medicine doctor and endocrinologist, a comprehensive evaluation was undertaken in the structural heart valve clinic including discussions with oncology and

Timeline



Case presentation

A 63-year-old female with a past medical history of hypertension who was undergoing treatment for a well-differentiated neuroendocrine carcinoma presented to our institution complaining of 3 months of progressive lower extremity oedema. Her physical exam

cardiothoracic surgery as to the potential and feasibility of repair options. Ultimately the patient was referred for surgical intervention of her dysfunctional tricuspid valve, and she underwent a surgical valve replacement with a 27 mm Epic porcine valve 1 month after TEE.

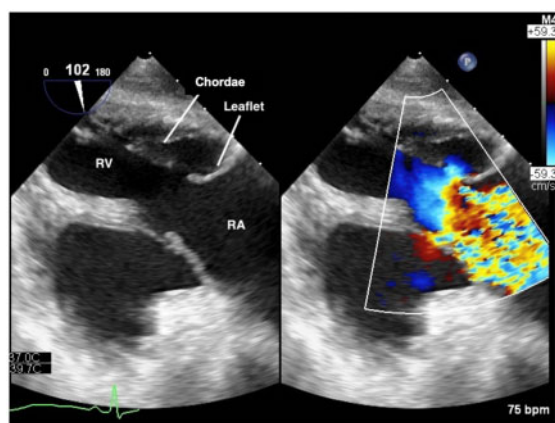


Figure 1 Transoesophageal echocardiogram demonstrating thickened and retracted leaflets.

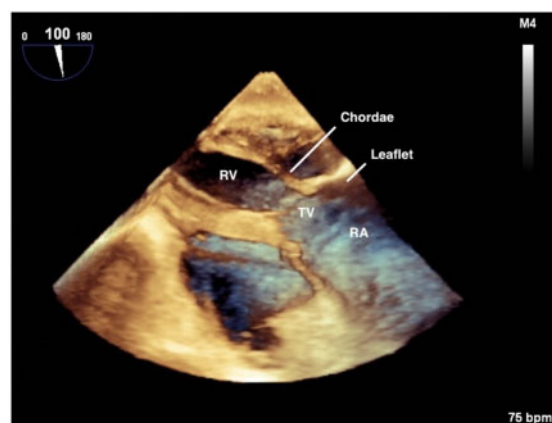


Figure 2 3D TEE demonstrating thickened and retracted leaflets and subvalvular apparatus.

Following surgery, our individual patient's valve was sent to the pathology department, and the only significant finding was the demonstration of fibrous plaques, thought to be correlated with an underlying endocrine tumour. Unfortunately, 3 days into the post-operative period, and prior to discharge, our patient suffered an in-hospital cardiac arrest and expired due to an unstable arrhythmia.

Discussion

The term 'carcinoid tumour' refers to a heterogeneous group of neuroendocrine neoplasms most often found in either the gastrointestinal (GI) tract or lungs, and can exist as an isolated condition or part of a larger familial syndrome such as multiple endocrine neoplasia type I (MEN I). Neuroendocrine tumours (NETs) are rare; however, recent reports have suggested an increasing incidence from roughly 1 in every 100 000 to 5 per 100 000 people in the USA.^{4,5} Within the GI tract, NETs are frequently located in the ileum, appendix, or rectum, and a certain subset can be extraluminal, involving pancreatic islet cells.⁶

Many of the clinical manifestations of NETs are attributed to the production of vasoactive substances including serotonin, prostaglandins, tachykinins, and histamine.^{7,8} These substances are typically metabolized by the liver, but, in the setting of hepatic metastases, they are able to enter the systemic circulation and result in the clinical findings associated with carcinoid syndrome.⁹ The syndrome is classically characterized by the constellation of cutaneous flushing, diarrhoea, and bronchospasm.

Carcinoid heart disease, which is typically right sided, has been reported to occur in association with the syndrome; however, only ~8% of NETs display this type of involvement,^{10,11} although rates as high as 50% have been reported.^{8,12} The pathology is mediated by plaque-like deposition of smooth muscle cells, myofibroblasts, and extracellular matrix substrates onto valves and endocardium, resulting in valvular dysfunction.¹³ This process is thought to be primarily mediated through the release of serotonin and its analogues, which activate 5-hydroxytryptamine 2B (5-HT2B) receptors in the heart.¹⁴

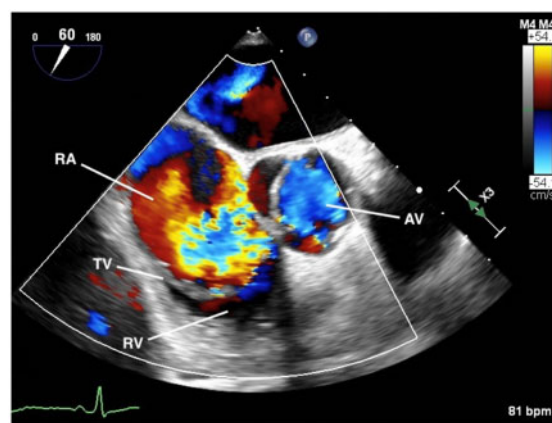


Figure 3 TEE with colour flow Doppler demonstrating severe tricuspid regurgitation.

The tricuspid and pulmonic valves are the most commonly affected, and can demonstrate progressively worsening regurgitation and eventual stenosis as the severity of the disease progresses.^{3,15} Frequently, the left side of the heart is spared due to the inactivation of vasoactive substances by the lungs, but reports of left-sided involvement have been documented in the presence of a right-to-left shunt or a bronchogenic carcinoid.³

Carcinoid syndrome and its associated complications can be a challenging diagnosis for physicians to make. Most often the diagnosis is made utilizing the detection of serotonergic metabolites in a patient's urine with the use of a 24-h HIAA (5-hydroxyindoleacetic acid) urine excretion level, often combined with serum studies investigating circulating levels of HIAA. In addition to metabolic studies, initial evaluation looking for the primary tumour can entail the utilization of transthoracic echo (TTE), cardiac magnetic resonance imaging (cMRI), computed tomography (CT), scintigraphy scanning, or positron emission tomography (PET). Unfortunately, these imaging modalities were not immediately available to our group in the

treatment of this patient. Surgical tissue excision and biopsy are often needed to confirm the diagnosis, as well as possible definitive treatment involving surgically addressing the tumour.^{10,15}

Management of carcinoid syndrome can be challenging, but is often achieved through the use of somatostatin analogues, such as octreotide or other adjunct chemotherapies.^{14,16} The treatment of carcinoid heart disease can be complex, and formal guidelines for management are lacking. There are limited data on ideal medical management for right-sided heart disease, but the mainstays of treatment include the use of (loop or thiazide) diuretics. Definitive therapy is achieved through surgical valve replacement; however, identifying the proper patients or the ideal timing has been shown to be challenging.^{17–19} It is advised to take a multidisciplinary approach to these patients involving cardiologists, cardiothoracic surgeons, oncologists, and endocrinologists. Carcinoid heart disease imparts significant morbidity and mortality, and surgical intervention should be considered when symptomatic disease exists. During the peri-operative period, these patients are often at risk for developing a carcinoid crisis, manifested by the presence of hypotension, flushing, and bronchospasm. In order to avoid this complication, it has been recommended that an octreotide infusion be employed during the pre-operative period, prior to surgical intervention, and subsequently continued for 48 h post-operatively.^{16,20}

Conclusion

The recognition, diagnosis, and treatment of neuroendocrine tumours and their associated syndromes are a rare but important subset of malignancies capable of affecting the cardiovascular system. Rapid diagnosis utilizing serum studies, CT scans, and echocardiography can help expedite the diagnosis and treatment of such rare conditions, and assist in the avoidance of complications due to the effects of circulating vasoactive substances. Despite its relatively well-recognized clinical symptoms, carcinoid syndrome and its associated heart disease still remains a challenging condition to manage and treat, often requiring the input of several subspecialties to treat the condition appropriately.

Lead author biography



Ali Ebrahimi is currently a general cardiology fellow at Northside Hospital with a focus on interventional and structural cardiology. He is also an associate researcher in the echocardiography department at the University of Alabama at Birmingham.

Supplementary material

Supplementary material is available online 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's next of kin in line with COPE guidance.

Conflict of interest: none declared.

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