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Carcinoid Heart Disease: A Critical Cardiac Complication of Neuroendocrine Tumors: A Case Report

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Abstract **Case Report**

Carcinoid heart disease (CHD) is a rare cardiac complication linked to advanced neuroendocrine tumors and carcinoid syndrome, predominantly affecting the right heart valves and potentially leading to right heart failure. The exact mechanisms behind CHD are not fully understood but are believed to involve various vasoactive substances released by the tumor. Managing CHD is complex because it requires addressing both the systemic malignancy and its cardiac effects. Early diagnosis and prompt surgical intervention are critical, as CHD is associated with increased morbidity and mortality. Valve replacement surgery can relieve right heart failure and may improve survival. We describe the case of a 58-year-old patient with a history of pancreatic neuroendocrine tumor and liver metastases, who was admitted with right-sided heart failure associated with carcinoid heart disease. This study provides a detailed review of the current literature on CHD, focusing primarily on its pathophysiology while also addressing clinical presentation, diagnostic approaches, and treatment options.

Keywords: Carcinoid Heart Disease (CHD), Neuroendocrine Tumors, Right Heart Failure, Pathophysiology, Valve Replacement Surgery.

INTRODUCTION

Carcinoid tumors are rare neuroendocrine cancers, often found in the gastrointestinal tract, particularly in the appendix and terminal ileum, but also in the bronchus and gonads. When these tumors metastasize to the liver, they release vasoactive substances such as serotonin, histamine, and prostaglandins into the bloodstream, leading to carcinoid syndrome with symptoms like facial flushing, severe diarrhea, and bronchoconstriction. Approximately 50% of patients with carcinoid syndrome develop carcinoid heart disease, where fibrous plaques form on the right side of the heart, primarily affecting the tricuspid and pulmonary valves, causing stenosis and regurgitation. Although left-sided valve involvement is rare, plaque formation is thought to be influenced by serotonin and other vasoactive substances [1-4].

We present the case of a 58-year-old patient with a history of pancreatic neuroendocrine tumor and hepatic metastases, who was admitted for right heart failure related to carcinoid heart disease.

CASE REPORT

This is a 58-year-old woman who has been postmenopausal for 5 years. She was diagnosed with a pancreatic neuroendocrine tumor (NET) and liver metastases 5 months ago, following the onset of diarrhea and abdominal pain. An abdominopelvic CT scan revealed a mass at the head of the pancreas consistent with a carcinoid tumor, three hepatic lesions indicative of metastases, and osteocondensing lesions in the L4 vertebral body. The diagnosis of NET was confirmed by a liver biopsy.

She has been undergoing oncology treatment for 2 months, which includes chemotherapy and somatostatin analogues. This treatment regimen consists of two courses, each spaced 4 weeks apart, with the first course administered 3 months ago.

Her illness began with the development of NYHA stage II dyspnea, accompanied by edema and digestive symptoms (diarrhea and abdominal pain). Her condition gradually worsened, with the dyspnea progressing to NYHA stage IV, along with exertional

hepatomegaly and abdominal distension. This progression, in the context of a general decline in her health, led to her referral by oncologists for a cardiac evaluation, including echocardiography and MRI.

The patient was admitted to the cardiology department and was hemodynamically stable, with a blood pressure of 125/65 mmHg, a heart rate of 65 bpm, a respiratory rate of 18 breaths per minute, and an oxygen saturation of 98%. Clinical examination revealed muffled heart sounds, pericardial friction rub, and signs of right heart failure, including jugular vein distension and hepatojugular reflux. Additionally, the abdominal examination showed hepatomegaly and ascites. The patient subsequently improved significantly with diuretic treatment, which led to a reduction in right-sided heart failure symptoms, decreased lower limb edema, resolution of ascites, and disappearance of jugular vein distension.

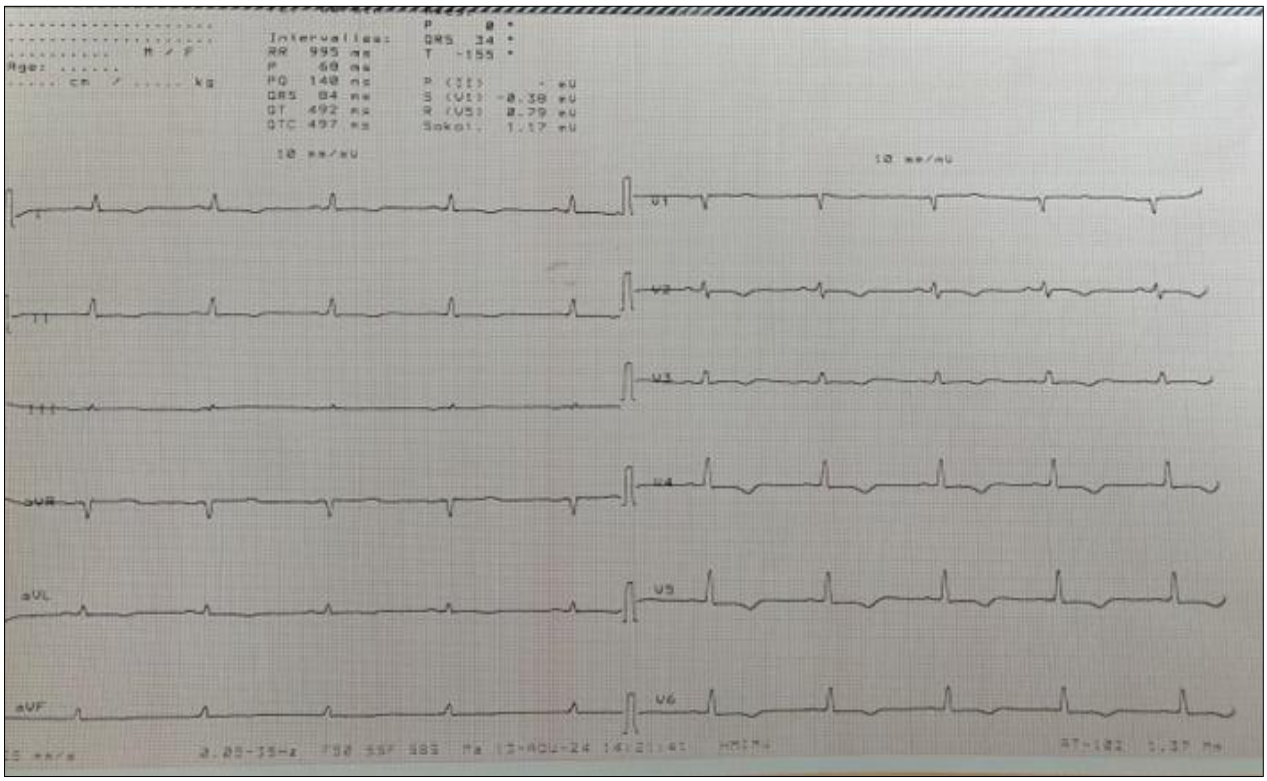

Figure 1: The EKG displayed a regular sinus rhythm at 60 bpm and diffuse low voltage

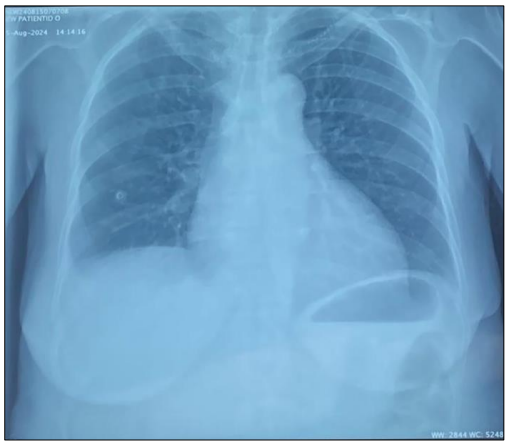

Figure 2: The chest X-ray reveals cardiomegaly with a prominent subdiaphragmatic peak and hilar overload, accompanied by pleural effusion

The biological work-up revealed hepatic cytolysis without hepatic cell failure and normal renal function. The patient underwent transthoracic echocardiography, which revealed significant dilation of the right ventricle (basal diameter of 52 mm) with dilation of the tricuspid annulus and an inverted RV/LV ratio > 1. Two-dimensional analysis of the tricuspid valve showed thickening of its leaflets, which were

retracted, rigid, and fixed in a semi-open position. The diastasis measured 9 mm and was responsible for low-velocity, narrow-spectrum tricuspid regurgitation on continuous Doppler, characteristic of laminar tricuspid insufficiency. The pulmonary valve, in turn, was mildly remodeled with limited opening, showing moderate stenosis (gradient of 12 mmHg) without dilation of the pulmonary artery. However, the right ventricle still maintained preserved function, with a TAPSE of 26 mm.

The left ventricle appeared non-dilated with preserved function: an ejection fraction (EF) of 58% and a global longitudinal strain (GLS) of -21.3%. Left ventricular filling pressures were elevated, with a dilated inferior vena cava and a minimal pericardial effusion.

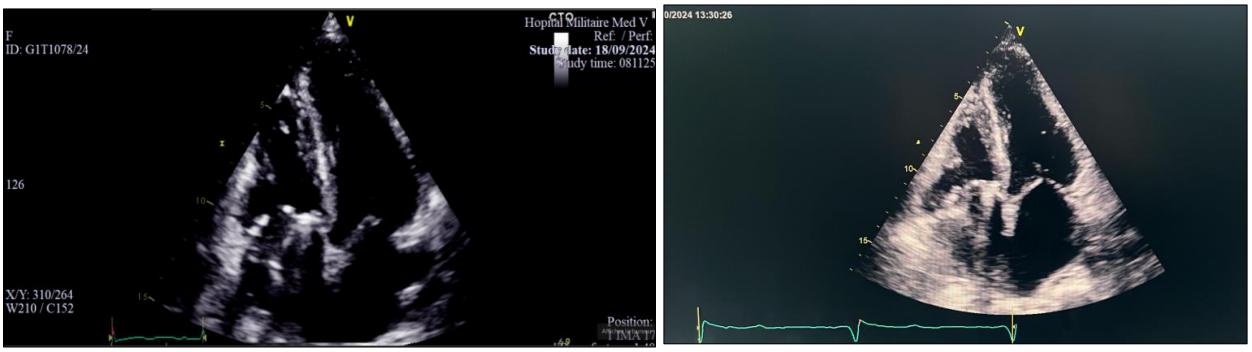

Figure 3: Echocardiographic images in apical four-chamber view showing a thickened tricuspid valve, fixed in a semi-open position

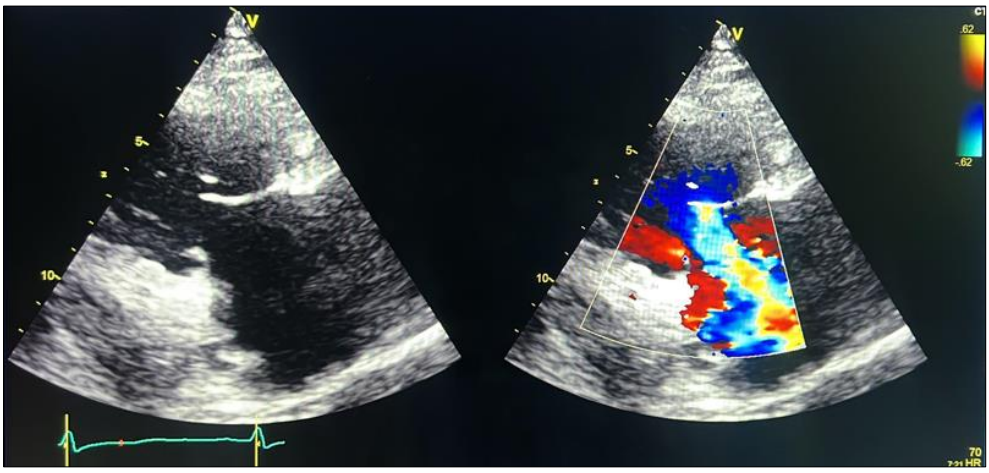

Figure 4: Echocardiographic image in parasternal long-axis view centered on the right chambers in two-dimensional mode and color Doppler showing carcinoid involvement of the tricuspid valve and regurgitation

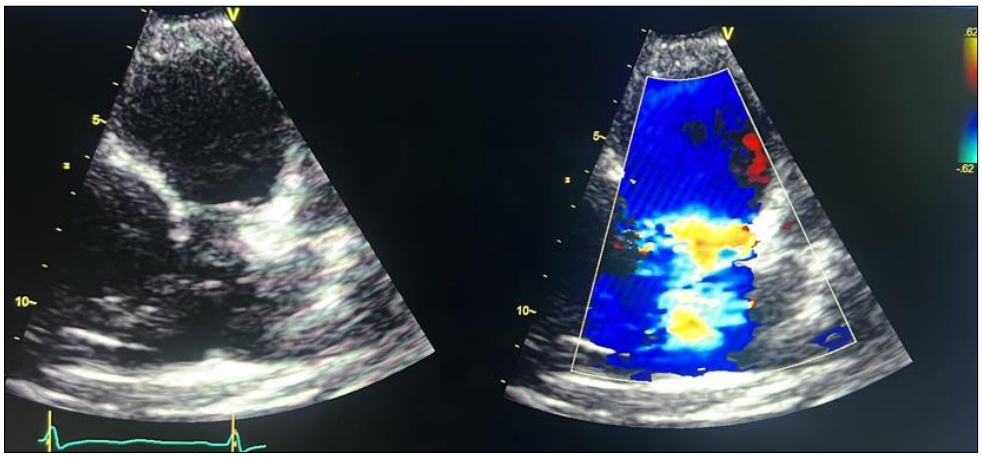

Figure 5: Echocardiographic image in short-axis view showing the pulmonary valve, which is mildly altered, with color Doppler aliasing indicating moderate stenosis at this level

Cardiac MRI confirmed that the right ventricle was dilated but maintained good kinetics and systolic function (RVEF of 60%), with an end-diastolic volume of 105 ml/m² and an ejection fraction of 60%. The right atrium was dilated with an area of 16.5 cm², while the left atrium measured 29.5 cm². No intracavitary thrombi were detected, although significant tricuspid regurgitation was present. Additionally, the pericardium showed mild effusion with a thickness of 9 mm in the inferior region, and there was moderate bilateral pleural effusion.

MRI sequences showed no abnormal myocardial signal on the T2 Fatsat sequence, no early perfusion defects, and no late enhancement on the corresponding sequences.

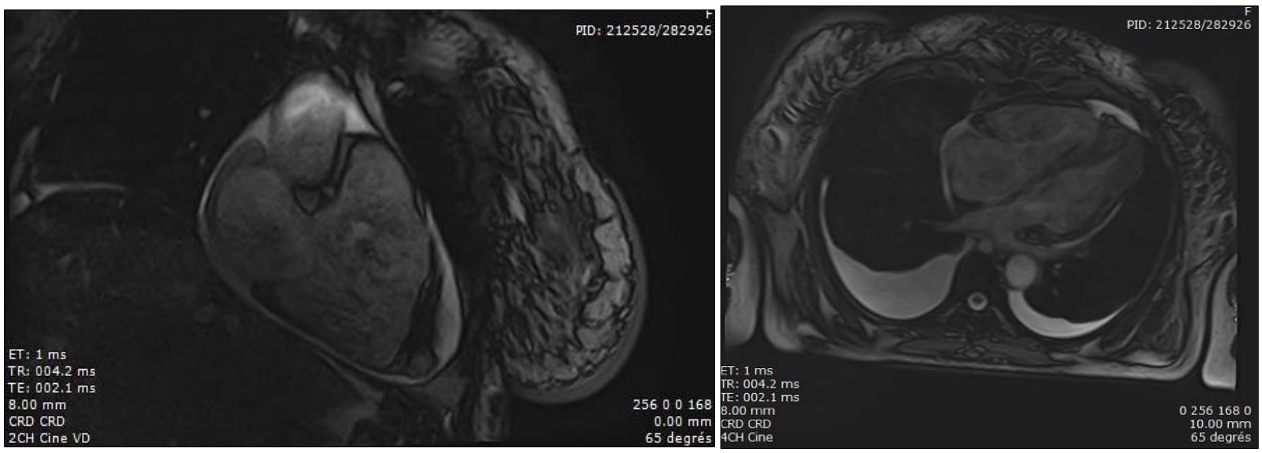

Figure 6: Cine-MRI (SSFP: Steady-State Free Precession), four-chamber view and two-chamber right ventricle view: showing dilation of the right chambers, apical hypertrophy of the left ventricle, and pericardial and pleural effusion

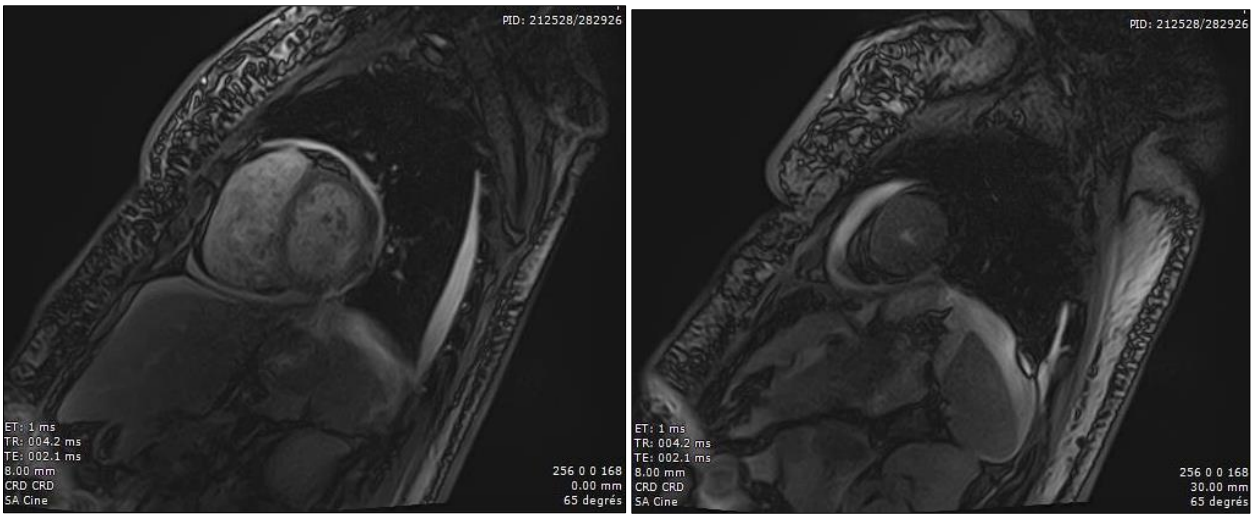

Figure 7: Cine-MRI (SSFP: Steady-State Free Precession), short axis at the apical and basal levels: highlighting the dilation of the right ventricle and localized hypertrophy at the apex of the left ventricle

The patient responded well to diuretic therapy, which included a high dose of diuretics and potassium supplementation. Following a multidisciplinary meeting with cardiologists, cardiovascular surgeons, and oncologists, and considering her favorable prognosis—demonstrated by the regression of symptoms such as diarrhea in response to chemotherapy, as well as her young age—the team decided to proceed with tricuspid valve replacement.

The patient underwent tricuspid valve replacement with a mechanical prosthesis immediately after completing her treatment with somatostatin analogues. The postoperative course was uncomplicated, marked by significant clinical improvement and the resolution of congestive signs.

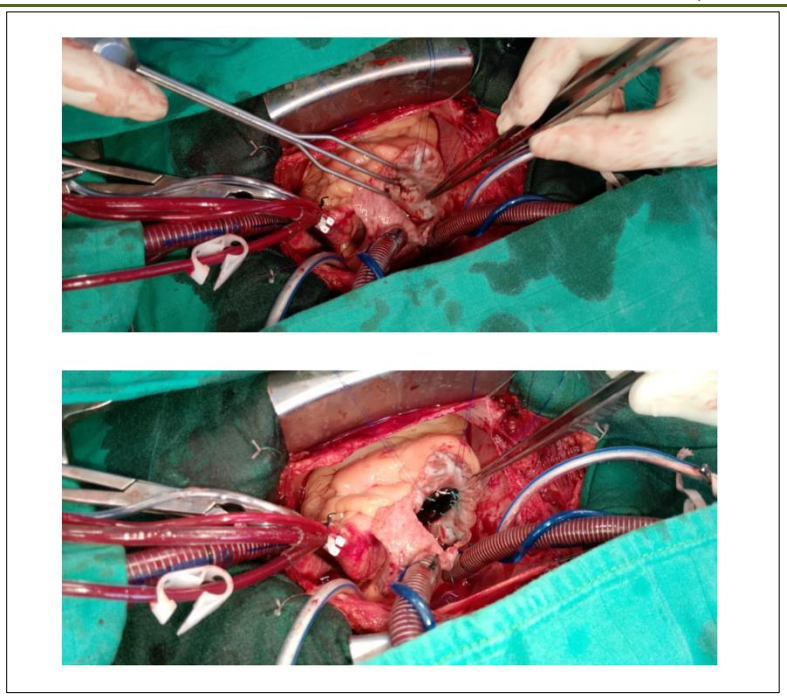

Figure 8: Image showing tricuspid valve replacement with a mechanical prosthesis

DISCUSSION

Pathophysiology of Carcinoid Heart Disease

Carcinoid heart disease results from the release of vasoactive substances by carcinoid tumors, including serotonin (5-hydroxytryptamine), histamine, tachykinins, transforming growth factor-beta (TGF-β), and prostaglandins [5]. Typically, these substances are broken down and inactivated by the liver and lungs. However, when carcinoid tumors metastasize to the liver, the right-sided cardiac structures are exposed to high levels of these hormones.

The exact cause of valvular damage in carcinoid syndrome is not fully understood. It is believed that serotonin and TGF-β stimulate fibroblast proliferation, leading to the deposition of fibrous plaques on the endocardium. These plaques, which consist of smooth muscle cells, myofibroblasts, extracellular matrix components, and an endothelial layer, accumulate on the valve leaflets, sub valvular apparatus, and cardiac chambers [6]. As a result, valve annuli become constricted, leaflets thicken, and the sub valvular structures may fuse [7], causing impaired valve function and regurgitation [8].

Patients with carcinoid heart disease have markedly elevated levels of serotonin, platelet serotonin, and urinary 5-hydroxyindoleacetic acid (5-HIAA) compared to those with carcinoid tumors without cardiac involvement [9, 10]. Moreover, serotonergic drugs and other medications that activate serotonin receptors have been associated with similar valvular lesions, further implicating serotonin in the development of carcinoid-related valvular disease [11].

Epidemiology

The frequency of Cushing's syndrome (CS) among patients with neuroendocrine tumors (NETs) has varied significantly over time, historically ranging from 3% to 74%, and currently fluctuates between 19% and 35%, depending on geographic location and treatment approaches [12]. The median overall survival for patients with CS is notably lower at 4.7 years, compared to 7.1 years for those without CS [13]. Tumor burden is a significant factor contributing to the higher mortality associated with CS. Additionally, carcinoid heart disease (CHD) is observed in approximately 20%–50% of CS patients and serves as a major prognostic indicator, with a 3-year survival rate of 31% for those with CHD, compared to 69% for those without CHD [14].

Clinical Manifestations

Carcinoid heart disease is characterized by progressive valvular damage leading to regurgitation, stenosis, right-sided heart failure, and metastatic carcinoid disease. In its early stages, the disease often presents with no symptoms and is typically diagnosed approximately 18 months after the initial diagnosis of carcinoid syndrome. Valvular involvement can range from mild thickening of the leaflets with minimal regurgitation to severe cases with fixed, retracted leaflets and significant regurgitation, sometimes accompanied by stenosis.

As tricuspid and pulmonic valve disease progresses, elevated right ventricular pressure causes ventricular dilation and right-sided heart failure, leading to peripheral edema and ascites. Hormone levels, particularly elevated 5-HIAA, are associated with the severity of the disease. Pathological examination

typically reveals thickened, white valves and sub valvular structures. In severe cases, carcinoid plaques may be visible on the heart's endocardial lining.

Left-sided cardiac disease is uncommon, affecting less than 10% of patients with carcinoid heart disease, due to the inactivation of vasoactive hormones in the pulmonary vasculature. However, left-sided disease can occur in patients with right-to-left shunts (such as patent foramen ovale or atrial septal defects), poorly controlled carcinoid syndrome with elevated hormone levels, or bronchopulmonary carcinoid disease. Metastatic cardiac involvement is rare, occurring in about 4% of patients with carcinoid syndrome.

Physical Examination

At the time of diagnosis, the physical examination may initially be normal. Early signs include murmurs associated with tricuspid and pulmonic valve regurgitation, and occasionally stenosis, along with elevated jugular venous pressure. A palpable right ventricular impulse may also be present. In more advanced cases, signs of right-sided heart failure, such as lower extremity edema, ascites, and hepatomegaly, may develop.

The physical examination has limited sensitivity, with studies showing that up to 37% of patients diagnosed with carcinoid heart disease via echocardiography may not exhibit detectable abnormalities during a clinical examination.

Treatment of Carcinoid Heart Disease

Managing carcinoid heart disease involves a combination of medical and surgical approaches, requiring a multidisciplinary team for optimal care. The goals of treatment are to alleviate heart failure symptoms, reduce circulating vasoactive hormone levels, and consider surgical valve replacement in advanced cases.

Medical Management

Medical treatment has two main objectives:

- Preventing progression to right-sided heart failure
- Managing symptoms and hypervolemia

For symptomatic carcinoid heart disease, the primary medical therapy involves somatostatin analogues, such as octreotide and lanreotide. These medications help improve symptoms and lower 5-HIAA levels in urine and serotonin levels in the blood. While these drugs do not reverse existing valvular heart disease [15], they are increasingly used in asymptomatic patients with elevated 5-HIAA levels to reduce hormone levels and potentially prevent the development of carcinoid heart disease.

Telotristat etiprate, a tryptophan hydroxylase inhibitor, is approved in conjunction with somatostatin analogues for treating diarrhea associated with carcinoid syndrome that is not controlled by somatostatin analogues alone. Although it is not yet clear whether telotristat etiprate slows the development or progression of carcinoid heart disease, studies suggest it can lower 5-HIAA levels, indicating it may help prevent the disease in patients with high serotonin levels [16, 17].

As tricuspid and pulmonary valve disease progresses, leading to right-sided heart failure, medical options become limited. Diuretics can manage symptoms by reducing cardiac preload, edema, and ascites. However, careful dosing is essential to avoid volume depletion, which can decrease cardiac output and potentially cause hypotension and acute kidney failure [18]. Additional measures, such as dietary and fluid restrictions and the use of compression stockings, can help minimize the need for diuretics.

Surgical Management

Valvular surgery may be appropriate for patients with well-managed metastatic disease but significant valvular damage who remain symptomatic despite medical therapy or exhibit right ventricular dysfunction [19], with at least 12 months of expected survival related to NET after surgery [20]. Valve replacement can effectively alleviate symptoms and improve outcomes. For those with severe symptomatic carcinoid heart disease, the 2-year survival rate is 40% for surgically treated patients, compared to 8% for those who do not undergo surgery [21]. Due to the complexity of the procedures, surgery should be performed at specialized medical centers by a team of experienced surgeons, cardiologists, and anesthesiologists familiar with carcinoid syndrome.

The optimal timing for valve surgery is not clearly defined. Patients with carcinoid heart disease should be referred for surgical assessment as soon as they present symptoms like fatigue, dyspnea, and edema or show asymptomatic signs of right ventricular dysfunction on echocardiography [14]. Tricuspid valve replacement is the most frequently performed procedure, though multiple valves may need replacement. The choice between biological and mechanical valve prostheses is debated. Biological valves might fail quickly due to ongoing plaque formation from high levels of vasoactive substances, while mechanical valves necessitate lifelong anticoagulation, which increases the risk of bleeding and valve thrombosis, especially in those with liver dysfunction. Decisions regarding valve type should be personalized, considering factors such as bleeding risk, life expectancy, and potential future treatments. Both options have their advantages and drawbacks, and these should be carefully discussed with the patient [6].

If a patent foramen ovale is present, it should be closed during surgery to prevent the development of left-sided carcinoid heart disease. Carcinoid syndrome can

complicate surgery, as anesthesia may trigger a carcinoid crisis by releasing large amounts of vasoactive hormones, which can cause severe hypotension, bronchoconstriction, and arrhythmias [22, 23]. To mitigate this risk, octreotide is generally administered before anesthesia and continued throughout the procedure and recovery until the patient is stable [24].

For patients who are not candidates for surgery, percutaneous catheter-based valvular procedures are being investigated. Although data on these techniques are limited, case reports indicate that percutaneous valves have been successfully used on native pulmonary valves affected by carcinoid heart disease [25], as well as on dysfunctional bioprosthetic pulmonary and tricuspid valves using a valve-in-valve approach [26, 27].

CONCLUSION

Carcinoid heart disease (CHD) is a rare but severe complication of advanced neuroendocrine tumors (NETs), leading to increased morbidity and mortality. The exact biological mechanisms behind CHD are not fully understood, although emerging evidence suggests that serotonin plays a crucial role in the destruction and dysfunction of heart valves. Early diagnosis and surgical intervention, before heart failure becomes severe, may improve patient outcomes. Gaining a deeper understanding of the molecular mechanisms driving fibrosis in CHD could help identify new targets for molecular therapies. Managing CHD is highly complex and requires a multidisciplinary team with extensive experience in the field.

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