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From Carcinoid Syndrome to Carcinoid Heart Disease: The Cost of Delayed Cardiac Surveillance

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Abstract

Carcinoid heart disease (CHD) is a serious cardiac manifestation of carcinoid syndrome (CS), characterized by progressive fibrotic degeneration of cardiac valves and right-sided heart failure. We report the case of a 72-year-old man with a history of metastatic small-intestinal neuroendocrine tumor and CS diagnosed four years earlier, who presented with worsening dyspnea and peripheral edema. Transthoracic echocardiography revealed characteristic findings of advanced CHD, including severely thickened, retracted, and immobile tricuspid and pulmonary valve leaflets, resulting in severe tricuspid and pulmonary regurgitation. Additional findings included right ventricular dilatation, severe biatrial enlargement, moderate mitral regurgitation, a small pericardial effusion, and a 7-cm ascending aortic aneurysm. The diagnosis was established based on the characteristic echocardiographic appearance and elevated N-terminal pro-B-type natriuretic peptide levels. Notably, no routine cardiological surveillance had been performed following the diagnosis of CS. The patient was managed conservatively with intravenous diuretic therapy and optimization of heart failure treatment. Following multidisciplinary evaluation, surgical intervention was not pursued because of the patient's advanced disease stage, clinical instability, and concomitant ascending aortic aneurysm, which collectively rendered him a prohibitive surgical candidate. His clinical course was subsequently complicated by acute kidney injury with progressive renal dysfunction and anuria, and he ultimately died during hospitalization. This case highlights the importance of regular cardiovascular follow-up in patients with CS, as delayed recognition of cardiac involvement may lead to advanced and potentially irreversible valvular disease. Early detection remains crucial for timely intervention and may improve clinical outcomes.

Categories: Cardiology, Cardiac/Thoracic/Vascular Surgery
Keywords: carcinoid heart disease, carcinoid syndrome, echocardiography, neuroendocrine tumor, pulmonary regurgitation, tricuspid regurgitation

Introduction

Carcinoid tumors are rare neuroendocrine neoplasms believed to originate from enterochromaffin cells located within the crypts of Lieberkühn throughout the GI tract. Less frequently, they arise in the lungs or ovaries. These tumors most commonly secrete serotonin (5-hydroxytryptamine), a biologically active vasoactive amine synthesized predominantly by enterochromaffin cells. Serotonin is derived from the amino acid tryptophan, and excessive release into the systemic circulation may result in carcinoid syndrome (CS). This clinical syndrome is characterized by secretory diarrhea, recurrent episodes of cutaneous flushing, bronchospasm, and, in advanced cases, the development of right-sided valvular heart disease, known as carcinoid heart disease (CHD) [1,2].

Approximately one-half of patients with CS eventually develop CHD, which is characterized by tricuspid valve regurgitation and pulmonary valve regurgitation or stenosis. In most cases, cardiac involvement manifests as right-sided heart failure, primarily attributable to severe tricuspid and pulmonary valvular dysfunction. Left-sided valvular involvement is uncommon and occurs in only 5-10% of cases [3]. The interval between symptom onset and the diagnosis of CHD is typically 24-28 months, although delays of up to five years have been reported. Furthermore, the mean time to surgical intervention is approximately 24 months, with the timing largely determined by the severity of cardiac symptoms and the extent of valvular involvement [4].

We present the case of a 72-year-old patient with a history of chronic atrial fibrillation, systemic arterial hypertension, and metastatic small-intestinal carcinoid disease, who presented with progressive heart failure symptoms. Echocardiography revealed characteristic carcinoid involvement of the right-sided valves, with severely thickened and retracted tricuspid and pulmonary valve leaflets, resulting in severe tricuspid and pulmonary regurgitation.

Case Presentation

A 72-year-old man was admitted to our hospital with progressive exertional dyspnea (New York Heart Association (NYHA) class III) and worsening peripheral edema over the preceding 10 days. His medical history included chronic atrial fibrillation, arterial hypertension, and metastatic small-intestinal neuroendocrine tumor with hepatic involvement, diagnosed four years earlier. He had previously undergone surgical resection of the primary tumor and was receiving treatment with lanreotide. Detailed oncological data, including tumor grade, Ki-67 proliferation index, hepatic tumor burden, and serotonin/5-hydroxyindoleacetic acid (5-HIAA) levels, were not available from the patient's oncology records. Furthermore, no formal oncological evaluation was performed during the index hospitalization. During this period, the patient had not undergone regular cardiological follow-up or screening for cardiac involvement.

On admission, his blood pressure was 145/89 mmHg, heart rate was 96 beats/min with an irregular rhythm, and oxygen saturation was 96% on room air. Physical examination revealed elevated jugular venous pressure, bilateral lower-extremity edema, a holosystolic murmur along the left lower sternal border, and a diastolic murmur over the pulmonary area. Laboratory evaluation revealed elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (2,180 pg/mL). High-sensitivity cardiac troponin I levels were within normal limits, while routine hematological and biochemical parameters showed no significant abnormalities (Table *1*). Electrocardiography showed atrial fibrillation without acute ischemic changes.

Parameter	Reference range	Day of admission	Day 5	Final measurement
Urea (mg/dL)	11-54	58	89	176
Creatinine (mg/dL)	0.60-1.20	1.24	2.68	5.94
High-sensitivity troponin I (ng/L)	0-11.6	18	28	45
NT-proBNP (pg/mL)	0-300	2,180	3,950	7,860

TABLE 1: Serial cardiac and renal biomarkers during hospitalization.

NT-proBNP, N-terminal pro-B-type natriuretic peptide

Transthoracic echocardiography revealed preserved left ventricular systolic function with an ejection fraction of 55% and severe biatrial enlargement. The tricuspid valve leaflets were markedly thickened, shortened, echogenic, and fixed in a semi-open position, resulting in the complete absence of coaptation (Figures *1*, *2*). Severe tricuspid regurgitation was present.

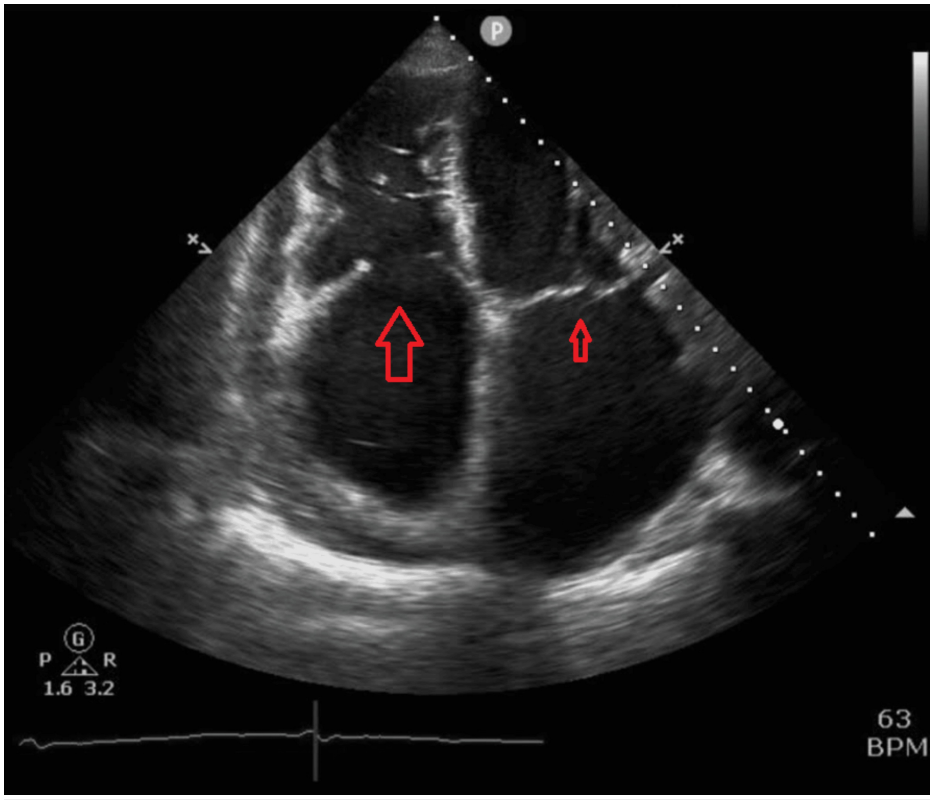


FIGURE 1: Transthoracic echocardiographic apical four-chamber view demonstrating severe biatrial enlargement and carcinoid-related fixation of the tricuspid valve leaflets in a semi-open position (large arrow), while the mitral valve remains closed (small arrow).

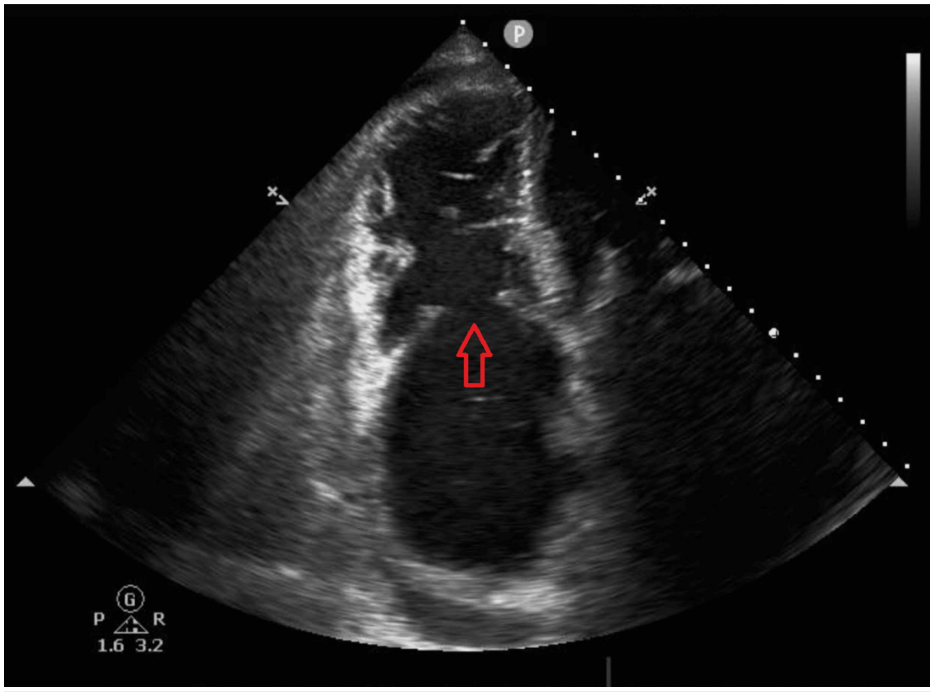


FIGURE 2: Transthoracic echocardiographic image obtained from a modified right ventricular-focused apical four-chamber view, demonstrating an unchanged position of the tricuspid valve leaflets during diastole compared with systole, indicating leaflet fixation (arrow).

The pulmonary valve cusps were similarly thickened and retracted, with markedly restricted mobility and severe pulmonary regurgitation (Figure *3*). Additional findings included right ventricular dilatation (basal diameter, 4.8 cm) with mildly impaired systolic function (tricuspid annular plane systolic excursion, 1.55 cm), moderate mitral regurgitation, a dilated inferior vena cava measuring 2.9 cm in diameter with no inspiratory collapse, a small circumferential pericardial effusion (0.9 cm), and an ascending aortic aneurysm measuring 7 cm in diameter.

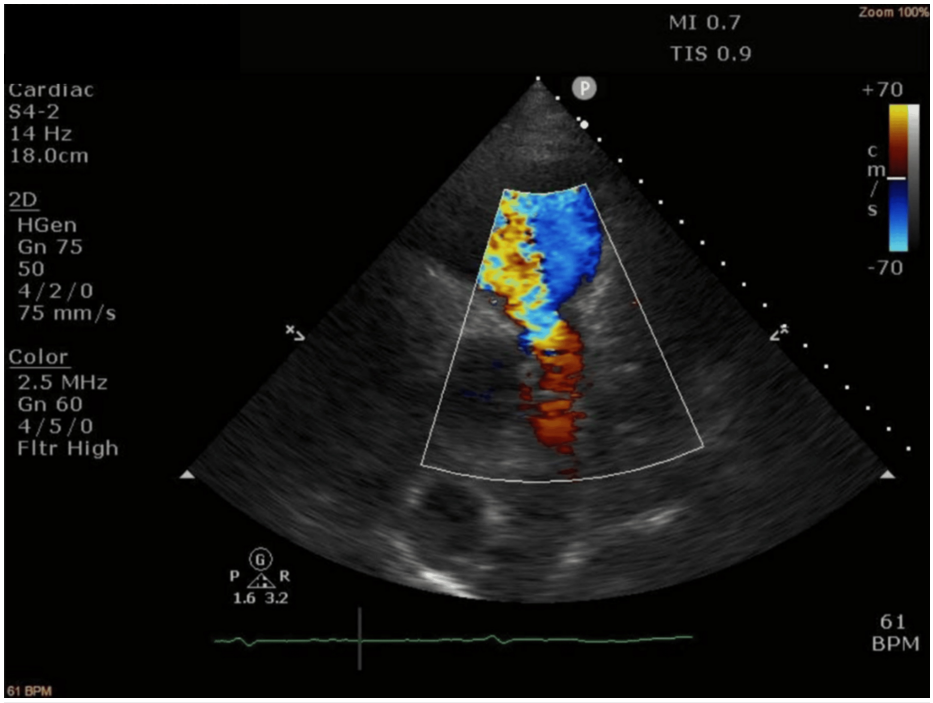


FIGURE 3: Transthoracic echocardiographic parasternal short-axis view with color Doppler demonstrating severe pulmonary regurgitation, consistent with pulmonary valve involvement in CHD.

CHD, carcinoid heart disease

Based on the characteristic echocardiographic findings and the patient's known history of CS diagnosed four years earlier, a diagnosis of advanced CHD was established. Notably, no routine cardiological surveillance had been performed during the interval between the diagnosis of CS and the current admission. Cardiothoracic surgical consultation was obtained. Following multidisciplinary evaluation, surgical intervention was not pursued because of the patient's advanced CHD with extensive fibrotic degeneration involving both the tricuspid and pulmonary valves and concomitant 7-cm ascending aortic aneurysm, which collectively rendered him a prohibitive surgical candidate. The patient was treated conservatively with intravenous diuretic therapy, optimization of heart failure medication, and continuation of anticoagulation for atrial fibrillation.

During hospitalization, the patient developed acute kidney injury with progressive deterioration of renal function and subsequent anuria. Despite supportive treatment, his clinical condition progressively worsened, and he ultimately died during hospitalization.

Discussion

Neuroendocrine tumors are rare neoplasms, with an estimated incidence of 2.5-5 cases per 100,000 population. CS affects multiple organ systems, including the liver, lungs, GI tract, endocrine system, and cardiovascular system, as a result of bioactive substances secreted by neuroendocrine tumors [5]. CHD results from fibrotic plaque deposition on the right-sided heart valves, causing leaflet thickening, retraction, and distortion of the valvular and subvalvular structures, which ultimately lead to severe valvular dysfunction [6]. Our patient presented with advanced valvular involvement, exhibiting severe carcinoid-related degeneration of both the tricuspid and pulmonary valves, resulting in severe valvular regurgitation and right-sided heart failure.

Tricuspid valve regurgitation is the most common valvular manifestation of CHD, being present in virtually all affected patients. Typical echocardiographic findings include thickened, shortened, and retracted tricuspid valve leaflets with incomplete coaptation, often fixed in a semi-open position, which may also result in varying degrees of tricuspid stenosis. Pulmonary valve involvement is also frequent, with regurgitation and/or stenosis reported in the majority of patients. These valvular abnormalities progressively lead to right-sided heart failure, commonly presenting with peripheral edema, abdominal congestion, and reduced exercise capacity [7].

Advanced symptoms (NYHA class III/IV) and right ventricular dysfunction have been associated with worse

clinical outcomes [7]. The rapid deterioration of renal function observed in our patient was most likely multifactorial. Advanced right-sided heart failure with severe systemic venous congestion may have contributed to the development of cardiorenal syndrome, although the potential contribution of intensive diuretic therapy and progressive systemic disease cannot be excluded.

Although right-sided valvular involvement is the hallmark of CHD, other cardiac manifestations have also been reported. Left-sided valvular involvement may occur in a minority of cases (<10%) [8]. Other manifestations, including coronary vasospasm in the absence of significant coronary artery disease, cardiac arrhythmias, and, more rarely, metastatic infiltration of the myocardium, predominantly involving the ventricular walls, have been observed. The diagnosis of CHD is based on a combination of clinical findings, biochemical markers such as urinary 5-HIAA, chromogranin A, and NT-proBNP, as well as multimodality cardiac imaging. Transthoracic echocardiography remains the cornerstone of diagnosis, while transesophageal echocardiography, cardiac magnetic resonance imaging, and nuclear imaging techniques may provide additional structural and functional information [1,8]. In our patient, the diagnosis of CHD was primarily based on the characteristic echocardiographic findings and elevated NT-proBNP levels. Given the previously established diagnosis of CS four years earlier, no further diagnostic investigations were considered necessary to confirm cardiac involvement. Furthermore, the absence of regular cardiological follow-up may have contributed to the delayed recognition of cardiac involvement and the advanced valvular disease observed at presentation.

The management of CHD includes treatment of heart failure, control of the underlying neuroendocrine tumor and CS, and surgical intervention when appropriate [1,5]. Determining the optimal timing for surgery can be challenging, as cardiac symptoms often coexist with manifestations of advanced systemic disease, including hepatic and GI involvement. Valve replacement remains the definitive treatment for severe valvular dysfunction; however, the choice of prosthesis remains a matter of debate. Bioprosthetic valves are generally preferred and have been widely used in large surgical series, including the Mayo Clinic experience. Nevertheless, recurrent carcinoid-related fibrotic degeneration of bioprosthetic valves has been reported, raising concerns regarding long-term durability [1,9]. An additional finding in our patient was a 7-cm ascending aortic aneurysm. Although no evidence suggested a direct association with the underlying neuroendocrine tumor, its presence was considered during multidisciplinary assessment and further contributed to the patient's overall surgical risk.

Current guidelines recommend routine cardiovascular surveillance in patients with CS, including regular assessment of NT-proBNP and transthoracic echocardiography. Patients with elevated NT-proBNP levels (>260 pg/mL), cardiac symptoms, or evidence of disease progression should undergo echocardiographic evaluation, while those with established CHD require serial echocardiographic follow-up according to disease severity. Early surgical intervention, before the development of advanced right ventricular dysfunction and severe heart failure, is associated with improved symptomatic and clinical outcomes. In the present case, cardiac involvement was recognized only after the development of advanced right-sided valvular dysfunction and symptomatic heart failure [10]. Our case further highlights the importance of regular cardiac surveillance in patients with CS to facilitate prompt diagnosis and appropriate management of CHD. The subsequent development of acute kidney injury and the patient's in-hospital death underscore the potentially severe consequences of delayed recognition of CHD.

Conclusions

CHD remains a potentially devastating complication of CS, often leading to advanced valvular dysfunction and right-sided heart failure. This case highlights the importance of regular cardiovascular surveillance following the diagnosis of CS, as delayed recognition may result in irreversible valvular damage and adverse clinical outcomes. The development of acute kidney injury and subsequent in-hospital death in our patient underscores the potential consequences of advanced CHD.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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