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Case Report

# Carcinoid Heart Disease: Case Report and Literature Review

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## Abstract

We describe the case of a 51-year-old male patient, diagnosed with a neuroendocrine tumor, with liver metastases and carcinoid syndrome since January 2020. The patient had been treated with Somatostatin analogs (Somatuline), with a moderate decrease of tumor size. In September 2021, he presented aggravating dyspnea and symptoms of right heart failure. Transthoracic echocardiography revealed a right sided valvar involvement with thickened and restrictive leaflets of both tricuspid and pulmonary valves responsible for severe tricuspid and pulmonary regurgitations, associated with enlargement of right chambers suggestive of carcinoid heart disease.

***Keywords:*** *Carcinoid Heart Disease; Carcinoid Syndrome; Pulmonary Valve Stenosis; Tricuspid Valve Insufficiency; Neuroendocrine Tumors*

## Abbreviations

PHT: Pressure Half Time; LV: Left Ventricle; RV: Right Ventricle; SPECT-CT: Single-Photon Emission Computed Tomography; TAPSE: Tricuspid Annular Plane Systolic Excursion; 5-HT: 5-Hydroxytryptamine; 5-HIAA: 5-Hydroxyindoleacetic Acid

## Introduction

Primary diseases of the tricuspid or pulmonary valves are uncommon, Carcinoid heart disease is a rare, but interesting cause of tricuspid and pulmonary valve disease. Carcinoid heart disease is affecting 20 - 50% of patients with carcinoid syndrome. It is considered as a result of high circulating hormone levels, mainly serotonin, produced by carcinoid tumors. Cardiac involvement in carcinoid disease generally results in right-sided valvar lesions secondary to valvar fibrosis, associating tricuspid insufficiency and pulmonary insufficiency or stenosis. It is responsible of an increased morbidity and mortality in patients with carcinoid syndrome related to right heart failure [1,2]. Significant benefits in symptoms, overall quality of life and long term survival can be achieved when adequate medical treatment and early surgery, if needed, are established.

A case, regarding a hepatic carcinoid tumor with cardiac manifestations involving both tricuspid and pulmonary valves, is described.

## Case Presentation

We present the case of Mr L H, a 51 years old male patient diagnosed with a hepatic neuroendocrine tumor on Somatuline injections since January 2020.

The diagnosis of neuroendocrine tumor was made following an assessment of deterioration of general condition including asthenia, weight loss and anorexia associated with flash episodes of palpitations, diarrhea and facial congestion.

The biological assessment revealed a normal blood count, a normal hepatic and renal assessment as well as negative viral hepatic serology.

Thoraco-abdomino-pelvic CT scan showed an increased liver size with regular outlines and a rounded formation between segment VI and VII, this formation is poorly limited with polylobed outlines, it is hypo-dense enhanced at the periphery, delimiting a zone of central necrosis measuring (80 x 92.5 x 63.3 mm) with a low abundance peritoneal effusion. The anatomopathological and immunohistochemical study of the hepatic micro-biopsy was in favor of a hepatic localization of a neuroendocrine tumor with poorly differentiated architecture, "grade 2 of the WHO 2017". Somatostatin receptor scintigraphy (Octeroscan) revealed areas of hepatic hyper-fixation, correlated on the single-photon emission computed tomography "SPECT-CT" fusion sections with multiple sparse nodules, of secondary appearance. With a large mass of segment VI of the liver, of heterogeneous fixation, which may be related to a primary neuroendocrine location. And absence of any suspicious pancreatic, mesenteric or digestive fixation related to a primary neuroendocrine tumor. And absence of any ganglionic, bone or pulmonary fixation of a secondary nature. Upper and lower fiberoptic exploration of the digestive tract did not demonstrate any primary neuroendocrine tumor location.

The patient underwent Somatuline injections every 2 weeks since January 2020 with a 39% decrease in hepatic lesions size on the CT scan carried out in September 2021. However, the clinical course was marked by the installation of aggravating dyspnea with swelling of the lower limbs since September 2021, prompting a cardiology consultation.

Cardiac physical examination realized in November 2021 found signs of right heart failure including edema of the lower limbs, turgor of the jugular vein, hepatojugular reflux without hepatomegaly or splenomegaly. Cardiac auscultation found an intense systolic murmur in the tricuspid foc and a diastolic murmur in pulmonary foc. The lymph node areas were free.

The electrocardiogram was registered in sinus rhythm with fine QRS complexes, without ST-segment changes. Chest X Ray showed a cardiomegaly.

Trans-thoracic cardiac ultrasound confirmed the carcinoid heart disease by showing damage to the tricuspid valve which was thickened with restriction of the movement of both anterior and septal leaflets responsible for a 13 mm coaptation defect with severe laminar tricuspid insufficiency without tricuspid stenosis (average gradient to 2.1 mmHg) (Figure 1).

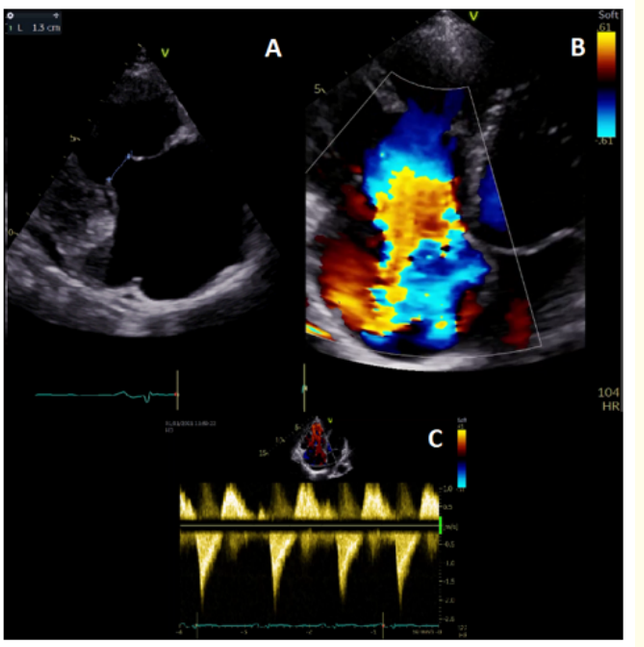


***Figure 1:*** *Transthoracic Echocardiography showing leaflets thickening and severe tricuspid regurgitation. (A) Parasternal long axis view of right chambers showing thickening of both anterior and septal tricuspid leaflets with a 13 mm coaptation defect. (B) Apical four chamber view with color flow doppler showing severe tricuspid regurgitation. (C) Continuous-wave Doppler profile of severe tricuspid regurgitation showing the characteristic dagger shaped spectrum with an early peak pressure and rapid decline.*

The pulmonary valve was also affected with thickening and restriction of movement of pulmonary valve leaflets responsible for a 5 mm coaptation defect with severe pulmonary insufficiency (PHT = 70ms) (Figure 2). The right chambers were very dilated with a RV/LV diameter ratio of 1.64 (Figure 3) with a normal longitudinal systolic function of the right ventricle (TAPSE at 20 mm). The inferior vena cava was dilated and non-compliant with reflux of the tricuspid insufficiency into the sus-hepatic veins (Figure 4). There was a small pericardial effusion and the left heart chambers and the aortic and mitral valves were normal.

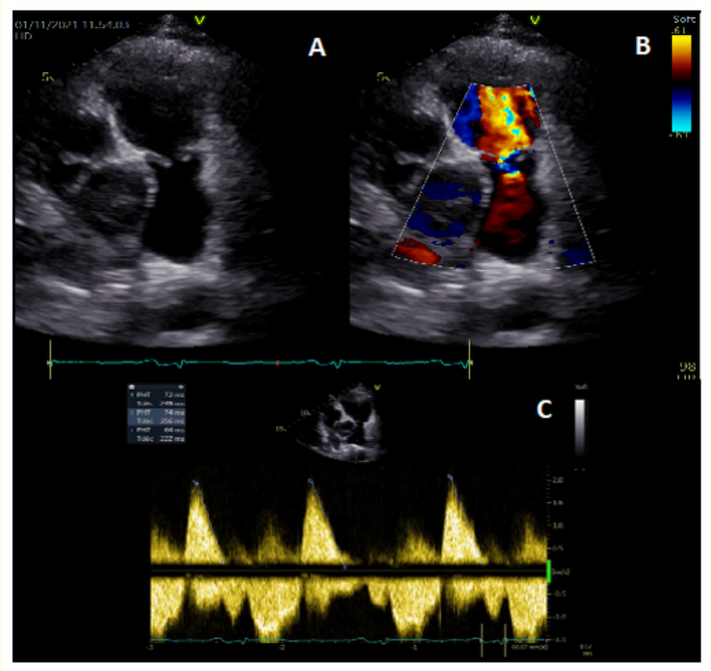


***Figure 2:*** *Transthoracic Echocardiography. (A) Parasternal short axis view showing thickening and restriction of pulmonary valve leaflets with a 5 mm coaptation defect. (B) Parasternal short axis view with color flow doppler showing severe pulmonary regurgitation. (C) Continuous-wave Doppler profile of severe pulmonary regurgitation showing the rapid deceleration rate with a PHT at 70 ms. PHT*: Pressure Half Time.*

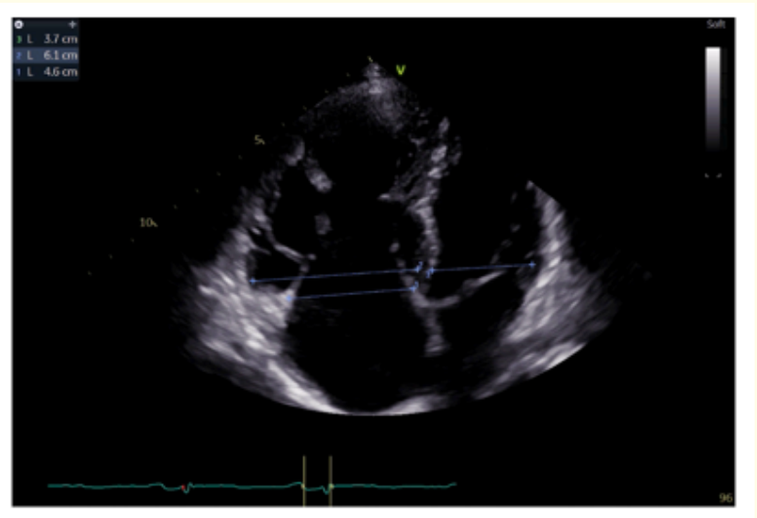


***Figure 3:*** *Transthoracic Echocardiography, Apical four chamber view showing right chamber dilation with a RV/LV diameter ratio of 1.64 with paradoxal septal motion. RV*: Right ventricle; LV*: Left ventricle.*

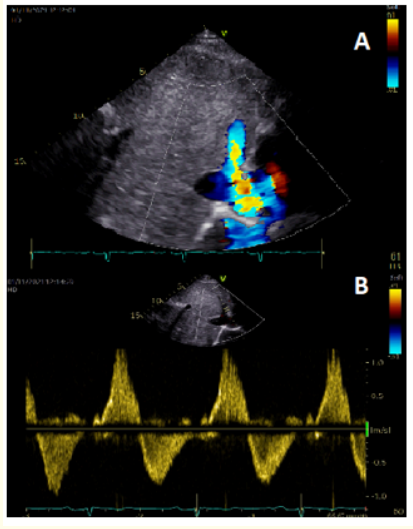


***Figure 4:*** *Transthoracic Echocardiography. (A) Subcostal view of the dilated and non-compliant inferior vena cava with reflux of the tricuspid insufficiency into the sus-hepatic veins. (B) Pulsed wave Doppler in the sus-hepatic veins showing a systolic reversed waveform.*

We prescribed loop diuretics in addition to Spironolactone as a treatment for right heart failure. We maintained the Somatostatin analogs (Somatuline) that he was already taking and the patient was referred to the cardiac surgery department for a double tricuspid and pulmonary valve replacement.

## Discussion

### Epidemiology and pathogeny

Carcinoid tumors are rare neuroendocrine malignancies located in 90% of cases in the gastrointestinal system, particularly the ileum and appendix. The incidence of carcinoid tumors is approximately 1 in 75 000 of the population [3].

Carcinoid syndrome occurs in 50% of carcinoid tumors and is characterized by facial flushing, intractable secretory diarrhea, and bronchoconstriction, as well as carcinoid heart disease that occurs in 50% of these patients. Ordinarily, the vasoactive tumor products (serotonin, histamine, tachykinins and prostaglandins) are inactivated by the liver, lungs, and brain, but the presence of hepatic metastases may allow large quantities of these substances to reach the right side of the heart without being inactivated by the liver. Exceptionally, carcinoid heart disease may present in carcinoid tumors without liver metastases or in primary ovarian carcinoid tumors in which 5-hydroxytryptamine (5-HT) is thought to reach the systemic circulation directly, bypassing portal circulation and the liver [4,5].

The vasoactive tumor products lead to fibrosis that involves preferentially the right heart including the tricuspid valve, pulmonary valve, cardiac chambers, venae cavae, pulmonary artery and coronary sinus. The fibrous reaction can cause either stenosis, regurgitation or both. Left side carcinoid heart involvement is less common due to inactivation of the vasoactive substances by the lungs. In case of left heart involvement, extensive liver metastases, bronchial carcinoid, or a patent foramen ovale should be suspected [6,7].

## Natural history

Carcinoid tumors are generally slow growing and follow a prolonged course of up to 20 or more years from the development of the carcinoid symptoms [2].

The occurrence of cardiac carcinoid involvement represents a turning point in the evolution of this pathology and a decline in clinical outcome since survival in patients without cardiac carcinoid involvement is approximately twice the survival rate compared those with carcinoid cardiac disease. However, the management of cardiac involvement could improve not only the symptoms but also the longevity [8,9].

## Clinical presentation

Carcinoid syndrome is characterized by flushing, diarrhea, and bronchospasm as well as labile blood pressure (hypertensive crises) and tachycardia. Patients with carcinoid syndrome can have a cardiac involvement in 50% of cases. The right sided valvar damage can be revealed by systolic murmur long the sternal edge caused by tricuspid regurgitation, associated with murmurs of pulmonary stenosis or regurgitation if present. Right heart failure is the result of severe tricuspid and/or pulmonary valvar damage.

## Diagnosis

The diagnosis of carcinoid syndrome is usually suspected by the clinical features and confirmed by identification of the primary tumor, localization of metastatic lesions, and detection of increased urinary excretion of the by-product of serotonin metabolism, 5-Hydroxy-indoleacetic acid (5-HIAA). The extent and severity of cardiac involvement is the main predictor of prognosis and clinical outcome [2].

Echocardiography is the key investigation for the diagnosis of carcinoid heart disease, whereas ECG and chest X-ray do not have a great diagnostic contribution. The most common findings in ECGs are sinus tachycardia, right bundle branch block, p pulmonale as well as non-specific ST segment changes. The ECG can be normal in 50% of cases. The chest *x* ray is also largely unhelpful, it can show cardiomegaly and can be normal in half of cases [9,10].

Transthoracic echocardiography plays a major role in the diagnostic and prognostic evaluation of cardiac involvement in patients with carcinoid syndrome. The echocardiographic aspects of valvar fibrosis is thickening, shortening and retraction of tricuspid and pulmonary valvar leaflets as well as sub-valvar tricuspid structures responsible for incomplete coaptation and tricuspid and/or pulmonary valvar regurgitation and less commonly pulmonary stenosis. Enlargement of right heart chambers is present in most patients with carcinoid heart disease. We can observe ventricular septal wall motion abnormalities such as paradoxical septal motion in 50% of cases [9]. Right ventricular function remains intact until quite late in the disease course [11]. The increasing elevation in right ventricular pressure and increasing size of the right atrium may lead to reopening of patent foramen ovale in severe carcinoid heart disease [12]. Left-sided lesions occur in up to 15% of all cases [13]. Because of the inactivation of serotonin as it passes through the lung, the involvement of left-sided valves is usually less severe than right-sided valvar lesions. Small pericardial effusions are present in up to 10% of cases. Myocardial metastases are rare [14]. When transthoracic echocardiography cannot adequately visualize structures, transesophageal echocardiography should be undertaken [15].

## Treatment

Patients with carcinoid syndrome are in an advanced stage of disease since metastatic spread of the tumor has already occurred, as a result, treatment tend to be palliative in these patients.

There are three main objectives for the management of patients with carcinoid syndrome: Treatment of heart failure, Reduction of vasoactive tumor products and Surgery for tricuspid and/or pulmonary valval damage.

Dietetic measures including salt and water restriction should be established. Diuretics are used to achieve fluid loss, mostly used diuretics are loop diuretics, but the association of loop diuretics and thiazide diuretic can be prescribed if additional diuresis is required. Digoxin can be prescribed to improve right ventricular contractility although the data on pure right sided heart failure are scarce [8].

Somatostatin analogs (Octreotide and Lanreotide) can be used as an antisecretory therapy in functioning *neuroendocrine tumors*, it has been noted to improve symptoms related to carcinoid syndrome including diarrhea and flushing. Lanreotide (or BIM23014, Angiopeptin and Somatuline) has the advantage of a less frequent administration compared to Octreotide which is administrated subcutaneously in 2 - 4 divided doses varying between 50 - 1500 µg/day [16-18].

Interferon-alpha can be used in association with somatostatin analogs. The use of leucocyte interferon-alpha can help controlling the secretion of tumor products by stimulating T lymphocytes and resulting in a notable reduction in tumor size and improvement of survival. However, there are no data to suggest that either interferon or octreotide can cause any regression of the cardiac damage caused by carcinoid disease [2].

Relief of symptoms can be achieved surgically by debulking the tumor, and sometimes, in those with hepatic metastases, by hepatic artery ligation or embolization [2].

The prognosis of patient with carcinoid heart disease is worsen by severe tricuspid regurgitation rather than carcinomatosis. Symptoms may be improved by balloon valvuloplasty in patients with tricuspid and/or pulmonary stenosis, although recurrent symptoms have been observed. Valve surgery remains the definitive treatment for right sided tricuspid and/or pulmonary valvar damage in patients with carcinoid heat disease. Therefore, consideration should be given to the suitability of a patient for valve surgery even in metastatic disease, unless the metastatic process is likely to lead to imminent death [8].

Early surgery should be indicated when carcinoid heart disease is diagnosed, since surgery delay can worsen right heart failure and affect surgery outcomes. Tricuspid valve repair is not usually feasible as the leaflets are so thickened and restricted with a strong risk of residual post-repair stenosis. The tricuspid valve can be replaced either by mechanical valvar prostheses or by bioprosthetic valves. Mechanical valvar prostheses are affected by the vasoactive tumor products and therefore durable. However, they present the problem of mandatory anticoagulation since carcinoid patients often have extensive liver metastases and therefore have a very high bleeding risk. Anticoagulation can be avoided by using Bioprosthetic valves, especially that the life expectancy of the patient is likely to be shorter than that of the valve. However, many surgeons fear secondary development of carcinoid lesions in bioprostheses and prefer the use of mechanical valves [2,8,19]. The optimal surgical management of pulmonary valve is still a subject of debate. Surgery of the pulmonary valve can include either valvectomy or valve replacement. If pulmonary valve regurgitation is left untreated, there would be right ventricular overload in the long run; whereas in patients with pulmonary valve replacement, the postoperative recovery appear to be more favorable [20]. In a recent small study of 22 patients, pulmonary valve replacement reduced the risk of right heart dilatation postoperatively, but more data are needed to optimise pulmonary valve surgery in carcinoid heart disease patients [21]. Transcatheter pulmonary valve replacement should be considered as an alternative approach avoiding open-heart surgery in the high-risk patients [22]. Surgical complications can include bleeding, carcinoid crises, right ventricular dysfunction, cardiac conduction disorders, renal failure and sepsis [23].

## Conclusion

Carcinoid tumors are rare neuroendocrine malignancies mostly arising within the gastrointestinal system. Carcinoid heart disease is a rare cause of right-side heart valve disease. It occurs in approximately 50% of patients with the carcinoid syndrome as a result of the effects of circulating vasoactive tumor products causing valvar fibrosis. It is associated to higher mortality and morbidity secondary to right heart failure. Echocardiography remains a reliable method for the definite diagnosis. Palliation of symptoms can be achieved with appropriate medical treatment including diuretics and Somatostatin analogs. Valvar surgery in selected patients with carcinoid heart disease can improve both quality of life and survival.

## Conflict of Interest

I declare no conflict of interest.

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