Scholars LITERATURE

International Journal of Integrative Cardiology

Mini Review

DOI: https://doi.org/10.47275/2690-862X-120
Volume 3 Issue 1

Carcinoid Heart Disease: A Brief Review

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Abstract

Carcinoid Heart Disease (CHD) is an uncommon presentation of carcinoid syndrome, but it ultimately occurs in most of these patients and is the major cause of morbidity and mortality in patients with CHD. CHD is primarily attributable to excessive levels of serotonin produced by carcinoid tumor, a neuroendocrine neoplasm usually located in the gastrointestinal or genitourinary tract. High levels of serotonin stimulate fibrosis resulting in fibrotic changes in the right-sided cardiac valves, causing tricuspid and pulmonic regurgitation and, to a lesser degree, stenosis of these valves. The disease is monitored by following urine levels of 5-hyroxyindoleacetic acid, the major metabolite of serotonin. The mortality of patients with CHD and heart failure is very high but recent advances in medical and cardiac interventional therapy have provided the potential for an improved outlook of patients with this disease.

Keywords: Carcinoid heart disease; Carcinoid syndrome; Carcinoid tumor; Endocrine disorder; Neuroendocrine tumor

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Citation: Jin C, Sharma AN, Thevakumar B, et al. (2021) Carcinoid Heart Disease: A Brief Review. Int J Integr Cardiol, Volume 3:1. 120. DOI: https://doi.org/10.47275/2690-862X-120

Received: February 28, 2021; **Accepted:** March 09, 2021; **Published:** March 15, 2021

Introduction

Carcinoid heart disease (CHD) is an uncommon manifestation of carcinoid syndrome, which is a rare endocrine disorder attributed primarily to the effects of serotonin (5-hydroxytryptamine) secreted by carcinoid tumors (Table 1) [1]. Few of these neoplasms are malignant. The incidence of carcinoid tumors is 1-5 of 100,000 persons [1-3]. Carcinoid tumors typically arise in the gastrointestinal and genitourinary tracts. The appropriate term for carcinoid neoplasm is a neuroendocrine tumor (NET) (Table 1). The major clinical manifestations of CHD are tricuspid and pulmonic regurgitation and, to a lesser degree, stenosis of these valves [1-3].

Pathophysiology

The pathophysiology of CHD is a result of elevated levels of serotonin produced by the NET (Table 1) [1-3]. Cardiac involvement is usually associated with hepatic dysfunction. Excessive serotonin can induce fibrosis, a process that can alter the structure of the right-sided cardiac valves by thickening, stiffness, and reduced mobility which result in tricuspid and pulmonary regurgitation and stenosis and lead to the pathophysiology and symptoms of CHD. Deposition of fibrous tissue may also include the right-sided papillary muscles, chordae, and ventricular walls.

Rarely, CHD may develop as a direct result of metastases to cardiac muscle. The valvular lesions are like those of ergot-alkaloid derivatives or (dex)fenfluramine [4]. Left-sided CHD is very unusual because serotonin is inactivated in the lungs [1-3].

Symptoms and Signs

The typical clinical manifestations of carcinoid syndrome are the triad of cutaneous flushing, diarrhea, and bronchospasm [1,4]. Less frequently, cardiac valvulopathy and restrictive cardiomyopathy of CHD are present early [2,4]. The onset of CHD symptoms is usually between ages 50-70 with exertional dyspnea and fatigue. More extensive symptoms of right-sided heart failure such as edema, ascites, pleural effusions, and cardiac cachexia may ensue. Major physical findings include murmurs of tricuspid and pulmonic regurgitation and stenosis, elevated jugular venous pulse with prominent v waves, a pan-systolic murmur of tricuspid regurgitation, and an early diastolic murmur of pulmonary regurgitation. Arrhythmias are a rare presenting feature of CHD, but it is necessary to consider them in patients with this disease.

Laboratory Findings

The final product of serotonin metabolism is 5-hydroxyindolacetic acid (5-HIAA), which is almost exclusively excreted in the urine. The

Table 1: Clinical Expressions of Carcinoid Disease.

Type	Features	Biomarkers
Carcinoid Tumor (NET)	Sites: GI and GU tracts, Bronchus	↑serum 5-HT and ↑24 h urine 5-HIAA levels
Carcinoid Syndrome	NET with metastases, primarily hepatic	↑↑serum 5-HT and ↑↑24 h urine 5-HIAA + systemic manifestations
Carcinoid Heart Disease	CS + Cardiac features	Same as CS + ↑NT-pro-BNP*

24h excretion of 5-HIAA provides a useful initial diagnostic test for carcinoid syndrome. A urinary level of this metabolite >300 mmol/24h helps identify individuals at risk for CHD [5]. Only post-treatment 5-HIAA levels independently predict the development or progression of CHD. Serum serotonin level is not a standard diagnostic test for carcinoid syndrome. False-negative serum tests for serotonin can result from the use of selective serotonin reuptake inhibitors whereas false-positive tests are caused by ingestion of tryptophan/serotonin-rich foods [5,6]. In patients with carcinoid syndrome, N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a sensitive and specific marker for the presence of CHD in the absence of other cardiac diseases [5]. It is uniformly recommended that all patients with carcinoid syndrome undergo 6 to 12-monthly clinical evaluations for symptoms and signs of valvular disease or heart failure by measurement of serum NT-pro-BNP (Table 1) [5].

The electrocardiogram in CHD usually has nonspecific findings such as ST-T changes but low voltage QRS complexes and PR prolongation may also be evident. The chest radiograph may reveal cardiomegaly with prominent right-sided chambers. Echocardiography is the mainstay of imaging for CHD. Tricuspid regurgitation is found in almost all patients with CHD and is characterized by thickened tricuspid leaflets, reduced mobility/immobility of right-sided valves, and tricuspid and pulmonic regurgitation and stenosis [7]. Metastatic carcinoid tumor to the heart is rare (<5%) [8]. Ventricular strain imaging has demonstrated reduced ventricular function that is predictably associated with a more advanced disease state. Cardiovascular magnetic resonance imaging is a useful adjunct for accurate assessment of right ventricular systolic function and detection of myocardial metastases [5].

Treatment

The goal of management for carcinoid syndrome and CHD is symptomatic relief and improved survival rather than definitive therapy and cure. The somatostatin analogs, octreotide, and lanreotide, have been effective in controlling symptoms of carcinoid syndrome [9,10]. Telotristat ethyl is an oral tryptophan hydroxylase inhibitor used in combination with a somatostatin analog for patients with inadequate response to the initial management of carcinoid syndrome with a somatostatin analog alone [10].

Liver-directed therapies include surgical resection, cytoreductive therapy, radiofrequency ablation, and hepatic embolization. Diuretics must be used judiciously because of the potential to reduce cardiac output in patients with right ventricular dysfunction and valve disease. Only post-treatment urinary 5-HIAA levels have independently predicted the development or progression of CHD. Persistent elevations in urinary 5-HIAA levels (>100 mg/24 h despite therapy) have been independently associated with the development or progression of CHD. The median survival of advanced carcinoid syndrome is 12 to 30 months. The presence of CHD with heart failure is associated with a poor prognosis and median survival of 11 months; without treatment, most patients succumb within one year because of progressive heart failure [1,2,4 and 5]. In a pooled analysis of 10 retrospective studies with a total of 193 patients, valvular surgery, largely comprising tricuspid valve replacement, was associated with improved prognosis; median postoperative survival was 58 months (28-80 months) with significant symptomatic relief in most patients [11]. The operative risk was high, and the average 30-day mortality was 17% (1-63%).

Summary

CHD is a rare form of carcinoid disease with high mortality. Stemming from serotonin-induced fibrogenesis, CHD is characterized by severe right-sided valvular abnormalities and confirmed by echocardiography. CHD most often presents between ages 50-70 years as dyspnea and fatigue. Treatment should rely on controlling the underlying carcinoid syndrome and managing subsequent valvular abnormalities and heart failure. The advent of novel medical and interventional therapies for this disease afford potentially promising approaches for treatment.

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