BRIEF REPORT

Carcinoid Heart Disease in Patients With Bronchopulmonary Carcinoid

Tais De Jesus, MD,[a] S. Allen Luis, M.B.B.S.,[a] Jay H. Ryu, MD,[b] Julian R. Molina, MD, PhD,[c] Heidi M. Connolly, MD,[a] Joseph J. Maleszewski, MD,[d] Patricia A. Pellikka, MD[a,*]

[a]*Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota*
[b]*Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota*
[c]*Division of Medical Oncology, Mayo Clinic College of Medicine, Rochester, Minnesota*
[d]*Division of Anatomic Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota*

Received 8 March 2018; revised 1 June 2018; accepted 27 June 2018
Available online - 6 July 2018

ABSTRACT

Introduction: The prevalence of carcinoid heart disease (CaHD) in bronchopulmonary carcinoid and its relationship with left-sided valvular disease are unknown.

Methods: All patients with a pathologic diagnosis of bronchopulmonary carcinoid and echocardiography performed at our institution between 2001 and 2016 were retrospectively reviewed. Echocardiograms were reviewed for features of CaHD including valvular leaflet thickening and retraction with resulting regurgitation and/or stenosis.

Results: Bronchopulmonary carcinoid was present in 185 patients (age 67 ± 13 years, 63% female). Carcinoid syndrome was present in 7.7% and liver metastases in 10%. Echocardiographic features of CaHD were present in just 2 (1%) patients. A 62-year-old woman underwent resection of stage 1A bronchopulmonary carcinoid without carcinoid syndrome and also received 7 months dexfenfluramine therapy. During 15-year follow-up, mitral regurgitation decreased and tricuspid regurgitation remained stable, a course more consistent with diet-drug–related valve disease than CaHD. A 71-year-old woman status post-resection of a grade 1 hilar carcinoid tumor with carcinoid syndrome, liver metastases, and elevated 5-hydroxyindole acetic acid had typical thickening and retraction of tricuspid and pulmonary valves with severe regurgitation. The aortic valve was mildly thickened and retracted with mild regurgitation. She underwent tricuspid and pulmonary valve replacement and closure of a patent foramen ovale. Pathologic examination confirmed CaHD.

Conclusions: CaHD occurs in less than 1% of patients with bronchopulmonary carcinoid. Bronchopulmonary carcinoid was associated with neither CaHD in the absence of liver metastases nor left-sided valve involvement in the absence of patent foramen ovale.

Keywords: Valves; Carcinoid heart disease; Carcinoid syndrome; Echocardiography

Introduction

Bronchopulmonary carcinoid tumors are an uncommon malignant neuroendocrine neoplasm that represents 1% to 2% of lung cancer and 10% to 33% of all carcinoid tumors.[1] Carcinoid syndrome is a rare paraneoplastic syndrome characterized by flushing, diarrhea, and wheezing resulting from the systemic release of histamine, prostaglandin, and particularly, serotonin. This syndrome commonly develops when liver metastases are present.[2] Compared to carcinoid tumors of small bowel origin, bronchopulmonary carcinoid is more often localized and less likely to be associated with liver metastases.[1,2] Carcinoid heart disease (CaHD) develops in approximately 20% of patients with carcinoid syndrome and is associated with a worse prognosis. It is thought to be the result of chronic exposure to high levels of circulating serotonin, which causes valvular fibrosis with leaflet retraction and thickening.[3] CaHD typically affects the right-sided heart valves resulting in regurgitation, stenosis, or both. Left-sided valvular involvement has been observed in up to 15% of patients with CaHD and attributed to the presence of a patent

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Patricia A. Pellikka, MD, Division of Cardiovascular Ultrasound, Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, phone: 001(507) 266-7432. E-mail: pellikka.patricia@mayo.edu

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2018.06.023

foramen ovale (PFO), marked carcinoid activity, or bronchopulmonary tumor. The lower incidence of left-sided valvular heart disease was hypothesized to be a result of pulmonary deactivation of circulating serotonin metabolites by monoamine oxidases.[3,4] No prior study has reported the prevalence of CaHD in bronchopulmonary carcinoid. This study aimed to estimate the prevalence of CaHD in patients with bronchopulmonary carcinoid and to determine if it has a predilection for left-sided valves.

Clinical Material and Methods

A retrospective review of all patients with a pathologic diagnosis of bronchopulmonary carcinoid and an echocardiogram performed at our institution from 2001 through 2016 was conducted. All patients underwent chest computed tomography with inclusion of the liver and adrenal glands within the imaging field. When liver lesions were present, this computed tomographic scan was followed by either hepatic ultrasound or magnetic resonance imaging. The study was approved by the Institutional Review Board.

Echocardiograms performed within 30 days before or after the diagnosis of bronchopulmonary carcinoid were included. Echocardiographic features of CaHD were assessed according to literature.[5-7]

Patient characteristics are expressed as mean (SD), median (intraquartile range [IQR]) or number (%). Wilcoxon test was used to compare differences between nonparametric variables. A value of $p < 0.05$ was considered significant.

Results

The records of 513 patients with a pathologic diagnosis of bronchopulmonary carcinoid were reviewed to identify 203 patients who underwent echocardiography. Pathologic diagnosis was made by biopsy in 106 patients (52%) and by tumor resection in 97 (48%). After the exclusion of 19 patients with echocardiography more than 30 days before the initial diagnosis of bronchopulmonary carcinoid, 185 patients were included. Of these, 19 patients underwent echocardiography as part of their perioperative workup. In the remaining 166 patients, the median echocardiographic follow-up was 51.5 months (IQR: 9.3 to 91.2 months, maximum 358.6 months). Clinical characteristics are shown in Table 1. The median peak 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) was 5.2 mg/24 h (IQR: 3.5 to 6.7 mg/24 h) (normal $\leq$ 8 mg/24 h), 4.8 mg/24 h (IQR: 3.3 to 5.9 mg/24 h) in patients with liver metastasis, and 7.3 mg/24h (IQR: 5.4 to 68 mg/24 h) in patients with carcinoid syndrome.

Carcinoid tumor was the indication for echocardiography in 33 patients (18%). Other indications included cardiac symptoms (20%), coronary artery disease (14%), pre-operative assessment (11%), noncarcinoid valvular heart disease (10%), arrhythmias (6%), pulmonary hypertension (6%), pre-chemotherapy assessment (4%), nonischemic cardiomyopathy (4%), and other (7%). Echocardiographic features of CaHD were present in 2 (1%) patients. Neither had measurement of N terminal–pro-brain natriuretic peptide (NT-proBNP).

One patient was a 62-year-old woman who underwent resection of stage 1A bronchopulmonary carcinoid without carcinoid syndrome and also received therapy for 7 months with dexfenfluramine. 5-HIAA and chromogranin A levels were not measured. The tricuspid valve septal leaflet was mildly thickened and retracted with mild regurgitation and the mitral anterolateral leaflet was thickened and retracted with moderate regurgitation. During 15-year follow-up, mitral regurgitation decreased

Table 1. Clinical Characteristics of 185 Patients With Bronchopulmonary Carcinoid

Variable	Missing	Result, n (%)
Female	0	117 (63)
Age, y	0	67 ± 13
Current or prior history of smoking	0	88 (48%)
Carcinoid syndrome	2	14 (7.7)
Presentation	11	
Asymptomatic		98 (56)
Cough		31 (18)
Dyspnea		16 (9)
Hemoptysis		14 (8)
Ectopic hormone syndrome		5 (3)
Other		10 (6)
Chromogranin A, ng/ml	157	Median 274 (IQR: 110-774)
NT-proBNP, pg/ml	148	Median 531 (IQR 299-1707)
Treatment	1	
Surgical resection		145 (79)
Observation/octreotide		25 (14)
Chemotherapy		4 (2)
Radiotherapy		1 (0.5)
Surgery with chemotherapy or radiotherapy		6 (3)
Endobronchial resection		3 (2)
Pathologic type	3	
Typical		149 (82)
Atypical		33 (18)
Tumor stage	12	IA: 84 (48.6) IB: 12 (6.9) IIA: 23 (13.3) IIB: 6 (3.5) IIIA: 21 (12.1) IIIB: 1 (0.6) IV: 26 (15)
Size of tumor ≤2 cm	37	78 (53)
Liver metastasis	6	18 (10)

NT-proBNP, N terminal pro-brain natriuretic peptide; IQR, interquartile range.