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Metastatic Carcinoid Tumor to the Heart: Echocardiographic-Pathologic Study of 11 Patients

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OBJECTIVES We sought to investigate the clinical and echocardiographic (echo) characteristics of metastatic carcinoid tumor in the heart.

BACKGROUND Right-sided valvular dysfunction is the hallmark of carcinoid heart disease. Cardiac metastases are uncommon in carcinoid syndrome. Features of patients with metastatic carcinoid tumor involving the heart (MCH) have not been well described.

METHODS From 1985 through 1999, 11 patients (8 male, 3 female), mean age ± standard deviation, 58 ± 6 years, were seen who had pathologically confirmed MCH. All patients had echoes, which were reviewed retrospectively.

RESULTS All patients with MCH had carcinoid syndrome. The primary carcinoid tumor was in the small bowel in 83% of patients, and all patients had hepatic metastases. On pathologic review, the 11 patients had 15 MCH tumors. All metastases were intramyocardial. The MCH involved the right ventricle in 40%, left ventricle in 53%, and ventricular septum in 7%. The average size of macroscopic tumors was 1.8 ± 1.2 cm. Nine MCH tumors were detected by echo in 6 of the 11 patients (55%). Mean echo-detected tumor size was 2.4 cm (range, 1.2 to 4). All tumors noted by echo were well circumscribed, non-infiltrating, and homogeneous. In the 5 other patients, review of autopsy records revealed 6 macroscopic tumors, mean size 0.35 cm (range, 0.2 to 0.4), none detected by echo even retrospectively. Carcinoid valve disease was present in 8 of the 11 MCH patients. The tricuspid valve was affected in all 8 patients (73%), pulmonary valve in 7 (64%), and left sided valves in 4 (36%) All patients with MCH identified by echo had cardiac surgery, 3 primarily for carcinoid valve disease and 2 for non-carcinoid cardiac disease; in 1 patient, MCH was the primary indication for cardiac surgery.

CONCLUSIONS MCH is uncommon but can be easily identified by echo if tumor size is ≥1.0 cm. In patients without valvular dysfunction, MCH may be the only manifestation of carcinoid heart disease. A search for MCH should be an integral part of the echo exam in patients with carcinoid syndrome. (J Am Coll Cardiol 2002;40:1328–32) © 2002 by the American College of Cardiology Foundation

Myocardial metastatic cardiac tumors occur in 2% to 20% of patients with metastatic cancer. The most common primary tumors that metastasize to the heart are breast, lung, and malignant melanoma (1). Carcinoid tumors are rare, arising in 1.2 to 2.1/100,000 persons in the general population per year (2). Clinically, in 20% to 30% of patients the initial presentation results from peptide production, that is, carcinoid syndrome. The malignant carcinoid syndrome consists of flushing, gastrointestinal hypermotility (secretory diarrhea), bronchospasm, and carcinoid heart disease. The diagnosis of carcinoid syndrome is usually suspected by clinical features and confirmed by increased levels of the byproduct of serotonin metabolism, 5-hydroxyindoleacetic acid (5-HIAA). Right-sided valvular dysfunction is the hallmark of carcinoid heart disease. Although carcinoid tumors have been described in almost every organ, there are few reported cases of confirmed carcinoid metastasis to the heart (3–9). The overall incidence of myocardial carcinoid metastases among patients with metastatic carcinoid disease is about 4% (9). There have been no series reporting the clinical and tumor characteristics along with echocardiographic (echo) and pathologic features of metastatic carcinoid to the heart.

To further investigate the clinical and echocardiographic characteristics of metastatic carcinoid tumor in the heart, we reviewed the Mayo Clinic experience with carcinoid from 1985 through 1999. The echo database (243 patients), patient charts, pathologic records (15 patients), and autopsy records (45 patients) pertaining to carcinoid disease were reviewed. Specifically, we reviewed (1) the natural history of patients with metastatic carcinoid tumor to the heart, (2) the usefulness of echo in making the diagnosis, and (3) the clinical course of patients with myocardial metastases.

METHODS

Selection of patients. From 1985 through 1999, 243 patients with carcinoid heart disease were seen. Of these, 11 patients (8 male, 3 female; mean age ± standard of deviation, 58 ± 6 years) were identified who had pathologic confirmation of metastatic carcinoid tumor involving the heart. All patients had known carcinoid tumors, and all had echo evaluation for valvular carcinoid disease. Five patients had no echo evidence of metastatic carcinoid to the heart, and in these patients myocardial metastases were identified at autopsy.

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Abbreviations and Acronyms
5-HIAA = 5-hydroxyindoleacetic acid
MCH = metastatic carcinoid tumor involving the heart

Clinical and Laboratory Findings All patients' clinical records were reviewed, including initial presentation and subsequent course. All patients had chest radiography, electrocardiogram, urinary 5-HIAA levels, and comprehensive 2-dimensional and Doppler echo examination. All echoes were retrospectively reviewed.

Pathologic Findings Surgical pathologic and autopsy reports were reviewed to assess the gross and microscopic pathology. Microscopic slides were prepared with hematoxylin-eosin, Masson trichrome, and Verhoeff-van Gieson stains.

RESULTS

Clinical features. All patients had symptomatic malignant carcinoid syndrome, confirmed by increased levels of urinary 5-HIAA (Table 1). The mean urinary 5-HIAA level was 255 ± 181 mg/24 h (normal < 6 mg/24 h). All patients had 1 or more of the classic symptoms associated with malignant carcinoid syndrome—most commonly flushing, in 9 of the 11 patients (82%), followed by diarrhea in 8 (73%) and dyspnea in 6 (55%). Average patient age at diagnosis of carcinoid syndrome was 52 ± 10 years. The time from diagnosis of carcinoid syndrome to diagnosis of metastatic carcinoid tumor to the heart (either by echo or autopsy) was 5.6 ± 3.9 years. Three patients were alive at the time of this study. The average age of patients at death was 58 ± 11 years. The average time from diagnosis of carcinoid syndrome to death was 9.5 ± 4 years and that from diagnosis of metastatic carcinoid tumor to the heart to death 6.3 ± 5 years. In 5 of the 11 patients (45%), the diagnosis of metastatic carcinoid tumor to the heart was first made at autopsy. The primary carcinoid tumor was identified in all 11 patients (Table 1). All primary tumors were in the gastrointestinal tract; 9 (82%) in the ileum, 1 in the rectum, and 1 in the cecum. All patients had hepatic carcinoid metastases.

Surgical management. All patients with echo evidence of a cardiac tumor had cardiac surgery, with removal (n = 8) or biopsy of the carcinoid metastasis. Additional cardiac surgical procedures were performed in five patients; in three patients for carcinoid valve disease, in two patients for noncarcinoid cardiac disease (coronary artery disease in one patient and mitral valve prolapse with mitral regurgitation in the other), and in one patient for metastatic carcinoid tumor to the heart. Surgical removal of the tumor was accomplished in five of six patients (83%); the other patient had tumor biopsy.

Echocardiographic features. Nine metastatic carcinoid tumors to the heart were identified by echo in 6 of the 11 patients (55%). Two of these patients had multiple tumors; 2 tumors in 1 patient and 3 in the other. Four of the 9 tumors were located in the left ventricular myocardium, 4 in the right ventricular myocardium, and 1 in the interventricular septum. The mean echo-detected tumor size was 2.4 cm (range, 1.2 to 4 cm). All metastatic tumors noted by echo were well circumscribed, non-infiltrating, and homogeneous (Fig. 1). No metastases were pedunculated or mobile. All of these patients went on to have cardiac surgery.

In 5 of the 11 patients, 6 macroscopic tumors were noted on autopsy, with a mean size of 0.35 cm (range, 0.2 to 0.4 cm). None of these tumors was detectable by echo, even with retrospective review. The average time between echo examination and autopsy diagnosis of metastatic carcinoid tumor was 45 days (range, 1 to 193 days). Multiple microscopic tumors were present in 2 patients. Four of the 6 tumors were located in the left ventricle and 1 each in the right ventricle and the interventricular septum.

Carcinoid valve disease was present in 8 of the 11 patients (73%) (Table 2). The tricuspid valve was affected in all 8 patients, the pulmonary valve in 7 (64%), the mitral valve in 3 (27%), and the aortic valve in 2 (18%). Three patients had no evidence of carcinoid valve disease.

Systolic function was preserved, with an average ejection

Table 1. Clinical Features of MCH

Patient	Gender	Age at Carcinoid Symptom Onset, yr	Age at MCH Diagnosis, yr	Age at Death, yr	Time from Symptom Onset to Diagnosis, yr	Time from Symptom Onset to Death, yr	5-HIAA, mg/24 h	Site of Primary Tumor
1	M	45	53	59	8	14	472	Ileum
2	M	67	68		1		119	Ileum
3	M	52	61	62	9	10	642	Ileum
4	M	58	60	72	2	14	248	Ileum
5	M	62	62		0		220	Ileum
6	F	62	66		4		106	Cecum
7	F	42	45	45	3	3	420	Ileum
8	M	53	62	62	9	9	118	Ileum
9	M	34	39	39	5	5	78	Rectum
10	F	51	63	63	12	12	148	Ileum
11	M	53	62	62	9	9	235	Ileum
Average		52.6	58.2	58	5.6	9.5	255	

5-HIAA = hydroxyindoleacetic acid; MCH = metastatic carcinoid tumor to the heart.

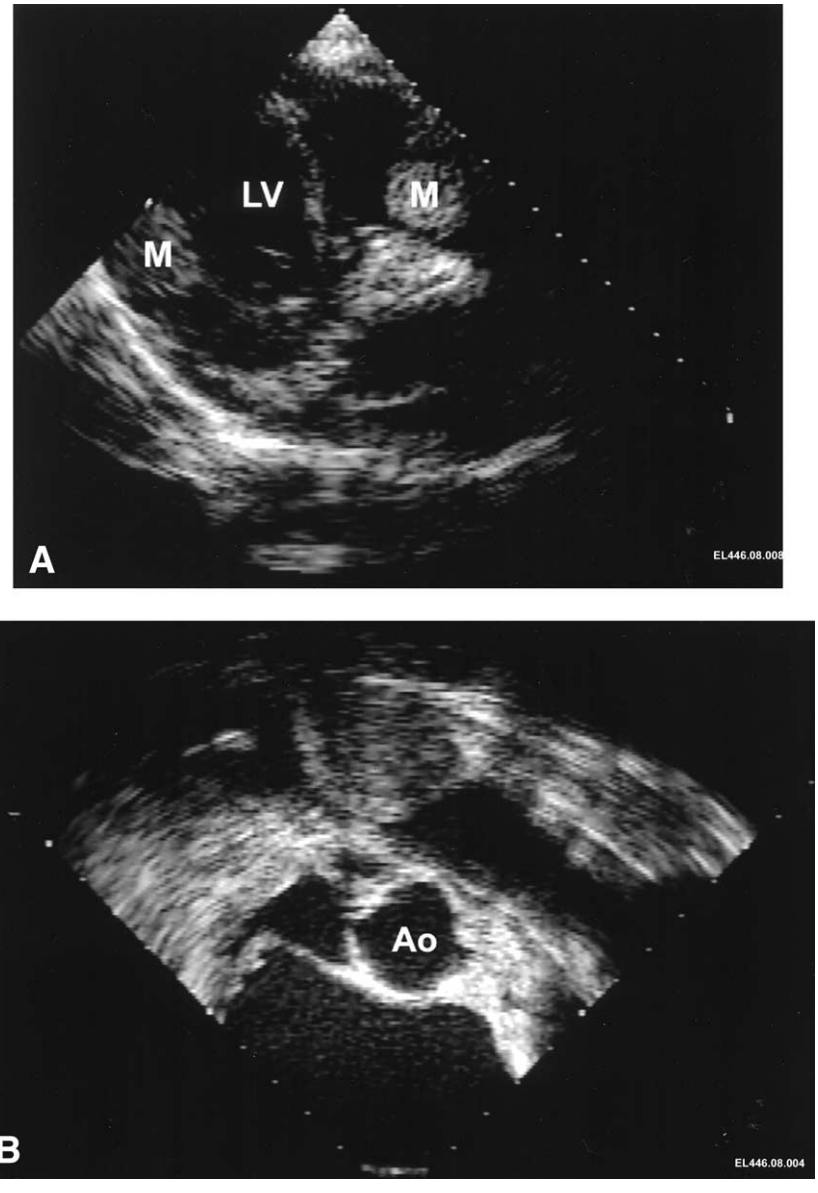

Figure 1. Echocardiographic features. **(A)** Metastatic carcinoid tumors (M) affecting the left and right ventricles. **(B)** Metastatic tumor affecting the right ventricular outflow tract. Ao = aorta; LV = left ventricle.

fraction of 62 ± 9%. A patent foramen ovale was detected by echo in 3 patients (1 by transesophageal and 2 by transthoracic echo). Two of these patients had evidence of left-sided carcinoid valvular heart disease.

Pathology. On pathologic review, the 11 patients had 15 metastatic carcinoid tumors (Table 2). All of the metastases were intramyocardial (Fig. 2). The average size of macroscopic tumors was 1.8 ± 1.2 cm (Fig. 3). The location of the 15 tumors was the right ventricle in 6 (40%), the left ventricle in 8 (53%), and the ventricular septum in 1 (7%).

The carcinoid valve pathology was consistent with gross thickening and presence of carcinoid plaques in the involved valves. Valve and metastases noted by echo were confirmed by pathologic review in all patients.

DISCUSSION

To our knowledge, it is the first series to describe the echo features of metastatic carcinoid tumor involving the heart. Of the 243 patients seen with carcinoid heart disease from 1985 through 1999, 11 (4%) were identified as having metastatic carcinoid tumor involving the heart. Carcinoid tumor infiltration of the heart as the only cardiac manifestation of carcinoid disease is a significant finding. It underscores the importance of a complete echo evaluation in carcinoid syndrome.

Left-sided valvular pathologic changes occur in fewer than 10% of carcinoid patients who have cardiac involvement (9). It is most commonly found among those with an

Table 2. Echocardiographic and Pathologic Features

Patient	Valvular Involvement	EF, %	PFO	No. of Masses	Location of Metastases		
					LV	RV	IS
Echo detectable							
1	T,P,M	65	No	2	1	1	
2	T,P	64	Yes	1			1
3	T,P	66	No	1	1		
4	None	68	No	3	2	1	
5	None	77	No	1		1	
6	T,P,A	70	Yes	1		1	
Subtotal				9	4	4	1
Not echo detectable							
7	T,P,M,A	60	Yes	2	1	1	
8	T,M	55	No	1	1		
9	None	60	No	1	1		
10	T,P	40	No	1	1		
11	T,P	60	No	1		1	
Subtotal				6	4	2	
Total/average		62.3		15	8	6	1

A = aortic; EF = ejection fraction; IS = interventricular septum; LV = left ventricle; M = mitral; P = pulmonary; PFO = patent foramen ovale; RV = right ventricle; T = tricuspid.

intracardiac shunt, which allows the serotonin-rich blood to enter the left heart chambers without first passing through the lungs. Left-sided valvular disease in carcinoid syndrome may also occur in the presence of a primary bronchial carcinoid. Occasionally, left-sided valvular disease is seen in patients who have severe, poorly controlled carcinoid syndrome with high levels of circulating serotonin. In fact as recently shown, patients with left-sided valvular heart in the absence of a patent foramen ovale the circulating serotonins were significantly higher (10). Left-sided carcinoid valvular disease is characterized by regurgitation rather than stenosis of the valve.

In this series of patients with myocardial metastases, left-sided valvular involvement was present in 36%.

The present study is the first to provide echo features along with pathologic correlation and clinical outcome of patients with this rare entity. The metastatic carcinoid tumor has a recognizable appearance and can be readily detected by echo, provided that the tumor is at least 1.0 cm in size. Metastatic carcinoid tumor to the heart may be the only echo manifestation of carcinoid heart disease.

Clinically, the biochemical markers of disease (urine 5-HIAA), patient age, location of the primary tumor, duration of symptoms, and types of symptoms were similar to those of patients who historically had valvular carcinoid heart disease rather than to those who had carcinoid syndrome without cardiac involvement. In our series, patient survival from the time of diagnosis of carcinoid syndrome was 9.5 ± 4 years and diagnosis of metastatic carcinoid tumor was 6.3 ± 5 years. Comparison of survival

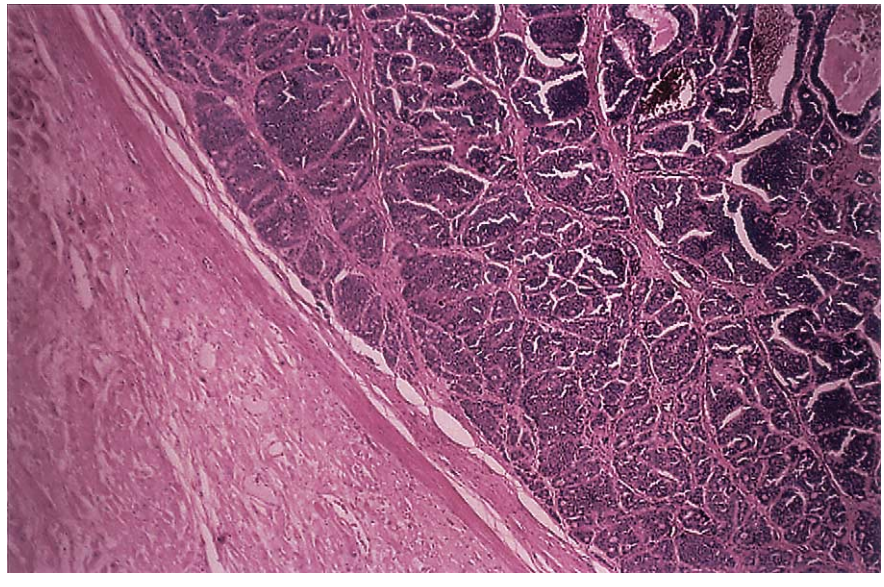

Figure 2. Metastatic carcinoid tumor to the right ventricle (Hematoxylin-eosin × 10).

Figure 3. Surgical specimen of metastatic carcinoid tumor to the right ventricle.

with historical controls was confounded by the small number of patients in our study, and five of our patients being diagnosed at autopsy.

Most of the patients with metastatic carcinoid tumors at autopsy or surgery had metastases involving the left ventricle, even though 8 of 11 patients had right-sided valvular disease. In two of the three patients without carcinoid valvular disease (by echo or pathology), the metastatic tumor was located in the left ventricle, perhaps because valvular carcinoid is related to the presence of active biochemical factors (such as serotonin). The presence and location of metastatic carcinoid tumor may also be related to the rheologic and mechanical factors in the milieu.

In conclusion, on echo evaluation, metastatic carcinoid tumor appears as a homogeneous, circumscribed, noninfiltrating mass affecting the left or right ventricular myocardium. Although metastatic carcinoid tumor is uncommon, it has echo characteristics that make it easily identifiable when it is 1.0 cm or larger. Metastatic carcinoid tumor may be the only manifestation of carcinoid heart disease. The comprehensive echo assessment of the patient with carcinoid disease should include a search for carcinoid cardiac metastases, even in the absence of carcinoid valvular disease.

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