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LETTER TO THE EDITOR

Carcinoid heart disease in an elderly female patient: the value of transthoracic echocardiography

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octreoscan

Carcinoid tumors are rare neuroendocrine tumors (NETs) with an incidence in the general population of 2.5—5.0/100,000 persons per year.[1,2] Carcinoid tumors appear to have increased in overall incidence over the past 30 years, possibly due to improvements in diagnostic technology and increased awareness.[2] Carcinoid tumors are most often located in the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%).[2] Up to 15% of patients may develop carcinoid syndrome, presenting clinically with cutaneous flushing, gastrointestinal hypermotility, and bronchospasm, caused by tumor release of serotonin and other vasoactive substances.[3] Approximately 50%-60% of patients with the syndrome present with carcinoid heart disease (CHD), a rare and unique manifestation caused by vasoactive substances secreted by metastatic tumor cells in the liver, leading to deposition of fibrous tissue in the endocardium and typically inducing abnormalities in the right side of the heart.[4] Studies suggest that the prevalence of CHD has decreased following the introduction of somatostatin analogues and other anti-tumor therapies designed to reduce the tumor load and the production of tumor secretory products.[5] In this study, we present the case of an elderly female patient in whom transthoracic echocardiography (TTE) provided sufficiently accurate assessment of valve structures to establish a diagnosis of CHD.

A 79-year-old woman presented to the emergency department with lower limb edema of two months' duration. The patient also described persistent diarrhea of nine months' duration that subsided two weeks before her presentation. Her past medical history was significant for arterial hypertension, restrictive lung disease, and a recently discovered (on abdominal computed tomography (CT)) hepatic mass that was presumed to be a hemangioma. Physical examination revealed blood pressure of 120/80 mmHg, a 3/6 systolic murmur mainly audible over the fourth intercostal space, liver edge palpable 3 cm below the right costal margin, a positive fluid wave sign, and lower limb edema up to the knee joint. A 12-lead ECG showed sinus rhythm and a heart rate of 70 bpm. The admission chest X-ray showed cardiomegaly and obliteration of the right costophrenic angle, compatible with a small pleural effusion. The abdominal ultrasound revealed a significant ascitic collection perihepatically and perisplenally, and an enlarged liver of 16 cm in diameter, with multiple nodules dispersed throughout the hepatic parenchyma, as well as a mass (10 cm in diameter) and a hepatic cyst (1 cm in diameter), both located in the right lobe. TTE revealed severe primary (organic) tricuspid and pulmonary regurgitation due to leaflet shortening and local thickening, with failure of systolic coaptation and incomplete fixation of both valve leaflets in a partially open position (Fig. 1, panels A—D). The right ventricle was dilated with signs of volume overload and the subxiphoid view revealed ascites and a hepatic mass (Fig. 2A).

To verify the presumptive diagnosis of CHD, further specific tests were ordered. Laboratory findings showed increased serum serotonin of 1,007 ng/ml (normal range 82—226 ng/ml), 24 h urinary serotonin of 485 μg/24 h (50—250 μg/24 h), 24 h urinary 5-hydroxy-indolacetic acid (5-HIAA) of 173 mg/24 h (0.7—8.2 mg/24 h), and plasma chromogranin-A (CgA) of 58.9 nmol/l (<4 nmol/l). The ^{111}In-pentetreotide scintigraphy (octreoscan) revealed two areas of radiotracer accumulation in the liver (Fig. 2B). The

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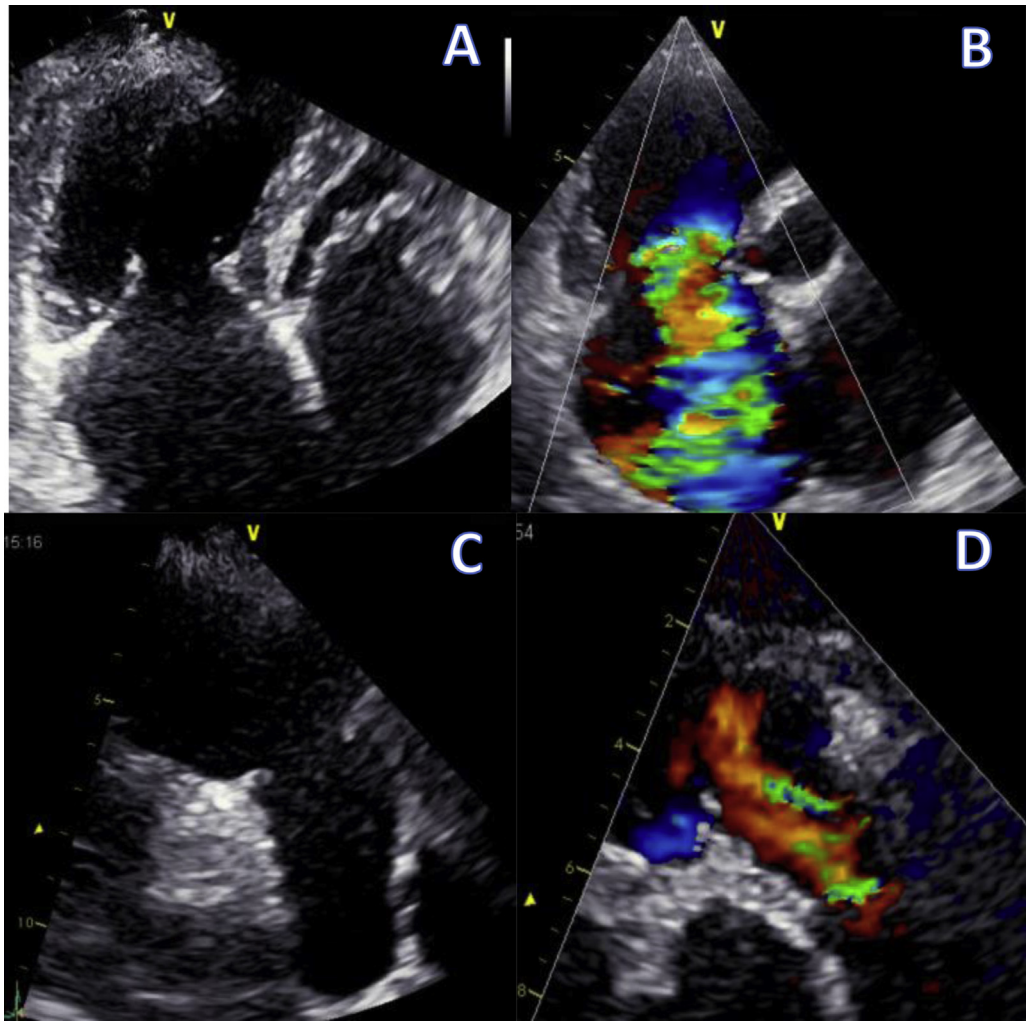

Figure 1 **A, C.** 2D views of the tricuspid and pulmonary valves. Fixation of both valves in an almost opened position with impressive leaflet shortening in the pulmonary valve. **B, D.** Same views with color Doppler displaying severe regurgitation through both valves.

fine needle liver biopsy that was performed showed a well-differentiated NET of the liver Grade I/Carcinoid, according the WHO classification. Microscopically, on H-E staining, tumor cells were arranged in solid, nested and microacinar patterns with vascular stroma (Fig. 2C). Tumor cells showed immunoreactivity for chromogranin (Fig. 2D) and CD56 (Fig. 2E), as well as Ki67 in <2% of cells (Fig. 2F).

The patient was treated with IV furosemide (120 mg/day), and amiloride (5 mg/day) per os and was discharged with clinical improvement twelve days later. The patient is currently under the care of the oncology service of a tertiary hospital and receives somatostatin analogue therapy (one injection every three months). She is doing fairly well, given that she has to undergo abdominal paracentesis for ascitic fluid removal every two months. The 5-HIAA levels have decreased to 120 mg/24 h and although the tumor diameter has also decreased (currently 7.5 cm), it has been characterized as non-resectable by the surgeons. The metastatic hepatic disease (not amenable to surgical treatment) and the severe symptomatic CHD (which is known to increase perioperative mortality substantially[3]) led the "Heart Team" to advise her not to undergo cardiac surgery.

Hepatic carcinoid tumors may mimic a hemangioma on CT, as was the case in our patient.[6] The diagnosis of carcinoid syndrome is usually suspected based on clinical features (cutaneous flushing, gut hypermotility with diarrhea, and bronchospasm with wheezing and shortness of breath) and confirmed by elevation of the by-product of serotonin metabolism 5-HIAA.[7] The 24-hour urinary collection of 5-HIAA is a specific and reproducible test that provides a reliable biological marker for the assessment of tumor activity and response to intervention.[4] Measurement of circulating plasma CgA has been established as a marker for the diagnosis of NETs for several years, and N-terminal pro-brain natriuretic peptide is an excellent biomarker of ventricular dysfunction.[5] Both of these markers are important for diagnosis in patients with CHD and are associated with a worse prognosis.[8] Octreoscan or positron emission tomography (PET) are used to stage patients with NETs.[9] Octreoscan identifies tumors by radiolabeled targeting of somatostatin receptors and is more sensitive for well-differentiated NETs, whereas 18F-fluorodeoxyglucose-PET ((18)FDG-PET) measures differential tissue glucose transport and demonstrates superior sensitivity for poorly differentiated NETs.[9]

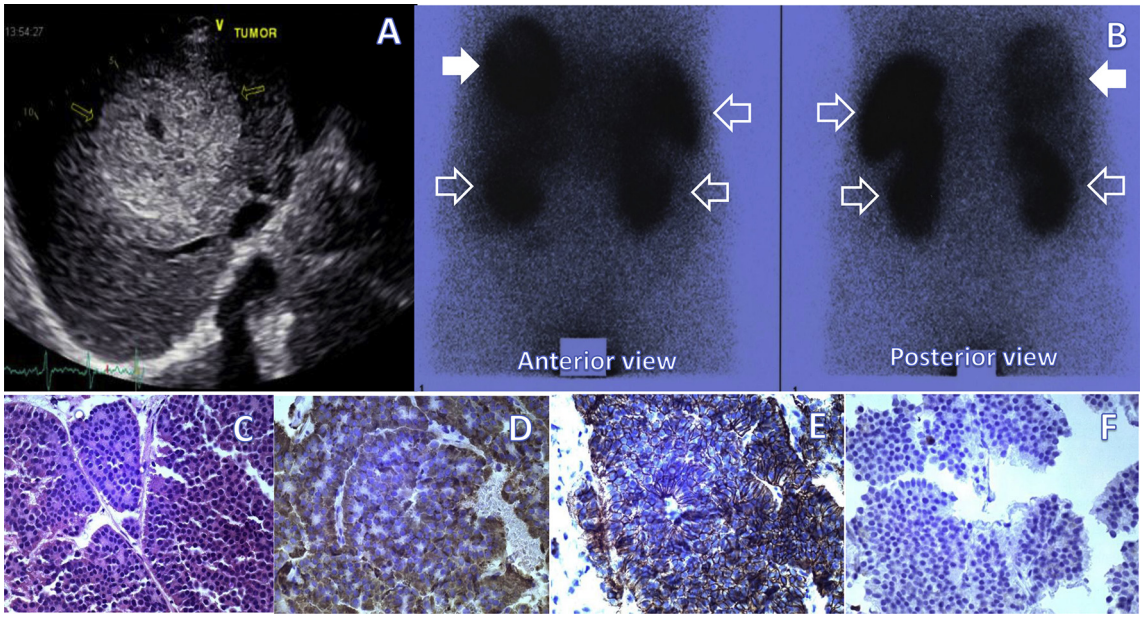

Figure 2 **A.** Subxiphoid view shows a hyperintense well-defined mass (arrows) within the right liver lobe. **B.** Octreoscan in anterior and posterior views showing two areas of radiotracer accumulation with central attenuation in the liver (solid arrows), as well as normal distribution of the radiotracer in the kidneys and spleen (open arrows). **C.** Photomicrograph showing tumor cells arranged in solid, nested and microacinar patterns with vascular stroma (H and E, ×100). **D—F.** Positive immunohistochemical staining for chromogranin (D), CD56 (E) and Ki67 (F) (one positive nucleus).

Up to 20% of patients with carcinoid syndrome present with CHD at diagnosis.[5] The echocardiographic features of CHD are well described, with the tricuspid and pulmonary subvalvular apparatus and valve leaflets being thickened and fixed, limiting leaflet excursion, preventing coaptation and leaving the valve in a semi-open position, which can cause a combination of valve regurgitation and stenosis.[4,5] In most patients, the tricuspid valve is affected, with or without pulmonary valve involvement, whereas pulmonary valve involvement is virtually pathognomonic. The right atrium and ventricle are typically enlarged. CHD is well tolerated initially, and patients may remain in NYHA class I, despite severe right-sided valve lesions. However, typical signs and symptoms of right heart failure appear as the disease progresses.[5] Approximately 15% of patients have valve lesions in the left heart, also characterized by diffuse leaflet thickening, although less severe than in the right heart. Small pericardial effusions occur in 10% of patients, but cardiac metastases are rare.[5]

Cardiac CT and magnetic resonance imaging can provide further important anatomical and functional information, especially for assessment of valve structure, right ventricular function and right chamber volumes.[7,10]

Regarding surgery, valve replacement should be the procedure of choice to treat right-sided lesions.[11,12] Although overall operative mortality in experienced centers has decreased to 10%, poor functional class (symptoms) better predicts adverse outcomes, meaning that presymptomatic surgical intervention correlates not only with better surgical outcomes but also with better long-term survival.[13] This further stresses the fact that the management of patients with CHD is complicated and requires a multidisciplinary approach involving specialists with broad experience in the field.[7]

The case presented in this report highlights the importance of TTE for the diagnosis of CHD and the accurate assessment of valve lesions.

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Disclosures

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