Delayed Presentation of Carcinoid Heart Disease and Subsequent Modified Healthcare Delivery in the COVID-19 Era

Alexandra N. Willauer, MD, Richard Hajjar, MD, Christina W. Estes, MD, and Kelly R. Laipply, MD, *Cincinnati, Ohio*

INTRODUCTION

Primary causes of tricuspid regurgitation (TR) account for 8%-10% of cases, whereas secondary causes account for the vast majority.[1,2] Carcinoid heart disease (CHD) is an important etiology of primary valvular disease for which early detection dramatically improves morbidity and mortality. However, establishing the diagnosis and creating an individualized treatment plan remains complex when utilizing several subspecialties and determining candidacy for surgical intervention. In the COVID-19 era, many patients experience delays in the evaluation and management of new and preexisting medical conditions that are both self-imposed due to fear of infection and secondary to an ever-strained healthcare delivery system. We describe the case of a 55-year-old man presenting with advanced CHD for which initial presentation was delayed due to fear of COVID-19.

CASE PRESENTATION

A 55-year-old man with a medical history of hypertension sought evaluation for a prominent, pulsatile vessel on the right side of his neck. He endorsed dyspnea on exertion, paroxysmal nocturnal dyspnea, bilateral lower extremity edema, and intermittent joint pain in his hands. These symptoms gradually progressed over the past two years. His edema was symptomatically managed with compression stockings and an oral diuretic, but an echocardiogram had not previously been obtained. He also reported chronic loose stools. His dyspnea on exertion had subacutely worsened 10 days prior to presentation concurrently with increased prominence of his neck pulsations, but he admitted he was hesitant to seek evaluation earlier due to the ongoing COVID-19 pandemic.

On presentation to the hospital, his blood pressure was 111/83 mm Hg, heart rate was 107 beats/minute, and oxygen saturation was 97% on room air. Pertinent physical exam findings included facial erythema, severe jugular venous distention bilaterally with prominent C-V waves, a grade 4 holosystolic murmur heard best at the left lower sternal border with an associated palpable thrill, and 2+ pitting edema of the lower extremities.

The patient's medical history included hypertension and benign prostatic hyperplasia. The patient had never used intravenous drugs. He was employed as a landscaper and noted that his dyspnea on exertion was worse with physical labor. He attributed his facial erythema to sunburn from working outside. His father had congestive heart failure, and his mother had a history of pancreatic cancer. There was no family history of connective tissue disease.

Initial laboratory results demonstrated a white blood cell count of 11.5 $\times$ 10^9/L (reference range, 3.8-10.8 $\times$ 10^9/L), high-sensitivity troponin of 6 ng/L (reference range, 0-20 ng/L), N-terminal pro b-type natriuretic peptide of 802 pg/mL (reference range, 15-125 pg/mL), and D-dimer of 2.38 μg/mL (reference range, 0.00-0.50 μg/mL). An electrocardiogram showed sinus rhythm with nonspecific ST-T wave changes. Imaging studies included a normal duplex ultrasound of the carotid arteries. A computed tomography (CT) pulmonary angiogram was negative for pulmonary embolism but did reveal enlargement of the right atrium (RA) and right ventricle (RV) with reflux of contrast into the inferior vena cava and hepatic veins (Figure 1). A subsequent transthoracic echocardiography (TTE) demonstrated a normal left ventricular ejection fraction of 55%-60%, dilation of the RA and RV with reduced systolic function, and a small pericardial effusion without tamponade physiology. The tricuspid valve was severely thickened with echodense leaflets fixed in a semiopen position and involvement of the subvalvular apparatus. There was primary severe TR and trivial stenotic physiology (Figures 2-4; Videos 1 and 2). Systolic flow reversal was appreciated on pulsed-wave Doppler interrogation of the hepatic vein (Figure 5). Diastolic septal flattening suggestive of RV volume overload was noted using M-mode echocardiography (Figure 6). The pulmonary artery systolic pressure could not be accurately estimated due to rapid equalization of RV and RA pressure in the setting of severe TR. Mild regurgitation of the pulmonic valve without evidence of stenosis was seen. The mitral and aortic valves were structurally normal. He incidentally tested positive for asymptomatic COVID-19 during routine hospital testing.

The patient underwent further workup for his tricuspid valve and right heart abnormalities. Rheumatologic studies revealed a positive atypical pANCA of 1:640 (reference range, <1:20) and SM/RNP of 3.2 (reference range, 0.0-0.9), and X-rays of the hands demonstrated bilateral thumb carpometacarpal joint osteoarthritis, lowering the suspicion for rheumatologic etiology. The patient did not have a history of intravenous drug use; furthermore, the blood cultures were negative and TTE did not show any vegetations.

From the Department of Internal Medicine, University of Cincinnati College of Medicine (A.N.W., C.E.), and Division of Cardiovascular Health and Disease, University of Cincinnati Medical Center (R.H., K.R.L.), Cincinnati, Ohio.

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Conflicts of Interest: None.

Correspondence: Alexandra N. Willauer, MD, Department of Internal Medicine, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML 0557, Cincinnati, Ohio 45267-0557 (E-mail: *Willauaa@ucmail.uc.edu*).

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VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE oriented in an apical four-chamber view showing a dilated right heart andsevere TR.

Video 2: Two-dimensional TTE with color Doppler oriented in the right ventricular inflow view showing turbulent tricuspid inflow with trivial stenotic physiology and severe TR.

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Oncologic workup revealed a serum serotonin of 1,493 ng/mL (reference range, 21-321 ng/mL), 24-hour urine serotonin of >300 mg/24 hours (reference range, 0.0-14.9 mg/24 hours), and chromogranin A of 806.7 ng/mL (reference range, 0.0-101.8 ng/mL). A CT scan of the abdomen demonstrated a mass within the root of the mesentery in the right lower quadrant and innumerable lesions in the liver concerning for metastatic carcinoid tumor (Figure 7).

While hospitalized, the patient was aggressively diuresed and had significant improvement in his lower extremity edema. Unfortunately, further advanced testing was delayed due to his COVID-19 positivity. He was scheduled for an outpatient liver biopsy, positron emission tomography (PET) scan, and right heart catheterization. Additionally, he was given outpatient referrals to endocrinology, surgical oncology, cardiology, and cardiothoracic surgery.

On outpatient follow-up, a gallium-68 DOTA-TATE PET/CT demonstrated increased activity within the liver, mesenteric lymph nodes, and a single lesion within the right lower quadrant (Figure 8). Percutaneous liver biopsy confirmed metastatic well-differentiated neuroendocrine tumor, grade 1. Pathology results were significant for positive synaptophysin and chromogranin in addition to less than 1% positivity for Ki-67. A right heart catheterization demonstrated elevated right-sided filling pressure (mean right atrial pressure, 15 mm Hg), normal pulmonary artery pressures, normal pulmonary capillary wedge pressure, and a low cardiac index (1.9 L/minute/m^2 by the Fick method). Due to rapid equalization of RV and RA pressure in the setting of severe TR, pulmonary artery systolic pressure can be underestimated by Doppler echocardiography. Thus, invasive hemodynamic assessment was performed and excluded pulmonary hypertension in this patient.

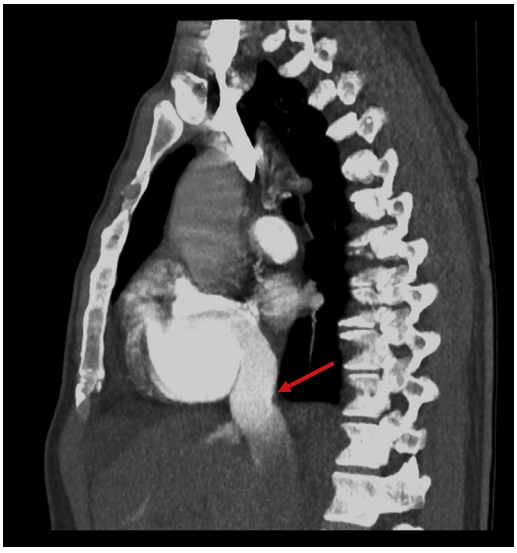

Figure 1 Contrast-enhanced CT of the chest, sagittal view, showing reflux of iodinated contrast into the inferior vena cava (*red arrow*).

The patient was initiated on octreotide therapy and remained on oral diuretics for symptomatic management. After consultation with a cardiac surgeon, surgical tricuspid valve replacement was deferred until the patient demonstrated a satisfactory response to chemotherapy. The patient was also referred to surgical oncology for consideration of tumor debulking but deemed not to be a candidate due to his metastatic disease burden. The patient was subsequently transitioned to lutetium-177 DOTA-TATE radiopharmacotherapy by endocrinology, and he has since been evaluated for minimally invasive endoscopic tricuspid valve replacement.

DISCUSSION

Carcinoid tumors are rare neuroendocrine tumors that most commonly arise from the gastrointestinal tract. Carcinoid tumors arising from the midgut may secrete vasoactive substances, including 5-hydroxytryptamine (5-HT), tachykinins, and prostaglandins.[3] Monoamine oxidase enzymes in the liver, lung, and brain convert 5-HT into the inactive metabolite 5-hydroxyindoleacetic acid, which is then excreted in the urine.[3,4] Disease confined to the gastrointestinal tract does not produce overt carcinoid syndrome as the vasoactive substances are largely removed from the portal venous system. Metastatic disease, however, releases vasoactive substances into the systemic circulation, resulting in the clinical carcinoid syndrome. Carcinoid syndrome is characterized by symptoms of flushing, diarrhea, and bronchospasm. Carcinoid heart disease is attributed to 5-HT-induced valvulopathies and classically affects the right side of the heart.[3,4] Stimulation of 5-HT receptors on cardiac valve results in plaque-like, fibrous endothelial deposits on the valve leaflets, subvalvular apparatus, atria, and ventricles.[3,4] These changes are classically seen in the tricuspid and pulmonic valves; left-sided lesions are less common given the presence of monoamine oxidase enzymes in the lung parenchyma. Although CHD is rare, this diagnosis should be considered in a patient presenting with symptoms of either TR or right heart failure and symptoms of CHD. Carcinoid heart disease typically presents late in the disease course, as premetastatic disease is often clinically silent. Still more, our patient cited his fear of the COVID-19 pandemic as the reason for his delayed presentation.

Comprehensive echocardiographic findings in CHD are well described.[5-7] Typically, the right-sided valves are affected, presenting most commonly with TR followed by pulmonic regurgitation and/or stenosis.[3,4] In mild cases, the valve leaflets become diffusely thickened, causing them to appear straightened and stiff with minimal dysfunction. With progressive disease, there is continued thickening of the leaflets and subvalvular apparatus.[4,6] As the chordae and papillary muscles of the subvalvular apparatus thicken, the chordae may become fused and shortened, resulting in varying degrees of reduced mobility with valvular retraction and tethering.[4,6] In severe cases, the valve leaflets become retracted and fixed in a semiopen position, resulting in a combination of regurgitation and stenosis.[4,6] Echocardiographic criteria used to grade severe TR include a dilated annulus with no valve coaptation or flail leaflet, large central jet encompassing >50% of the RA, vena contracta

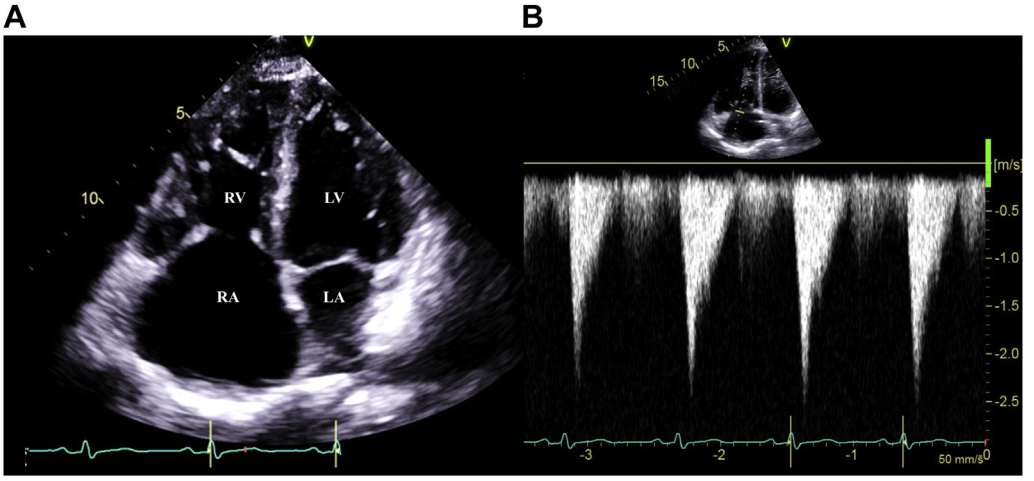

Figure 2 Two-dimensional TTE oriented in an apical four-chamber view showing fixed, semiopen tricuspid valve leaflets during systole **(A)**. Continuous-wave Doppler echocardiogram showing dense, triangular envelope of TR **(B)**.

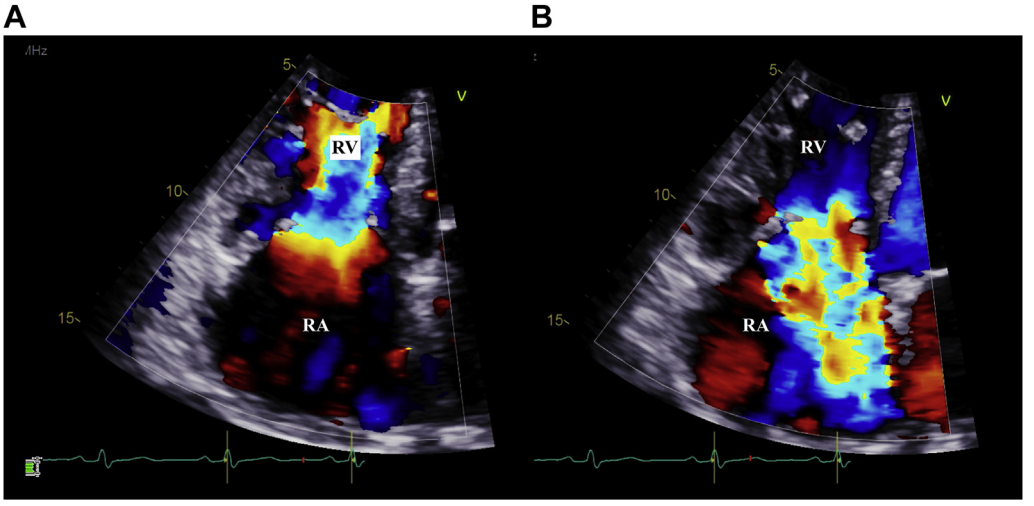

Figure 3 Magnified, color Doppler TTE oriented in an apical four-chamber view showing turbulent tricuspid inflow with trivial stenotic physiology **(A)** and severe TR **(B)**.

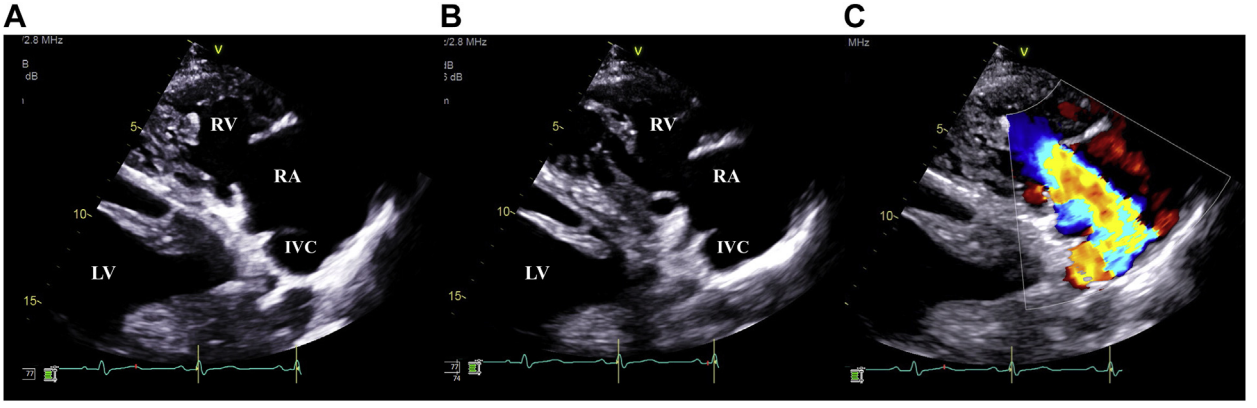

Figure 4 Two-dimensional TTE oriented in a right ventricular inflow view showing a thickened and fixed, semiopen tricuspid valve with minimal change between end systole **(A)** and end diastole **(B)**. Color Doppler revealed severe TR due to the leaflets being fixed in a semiopen position **(C)**.

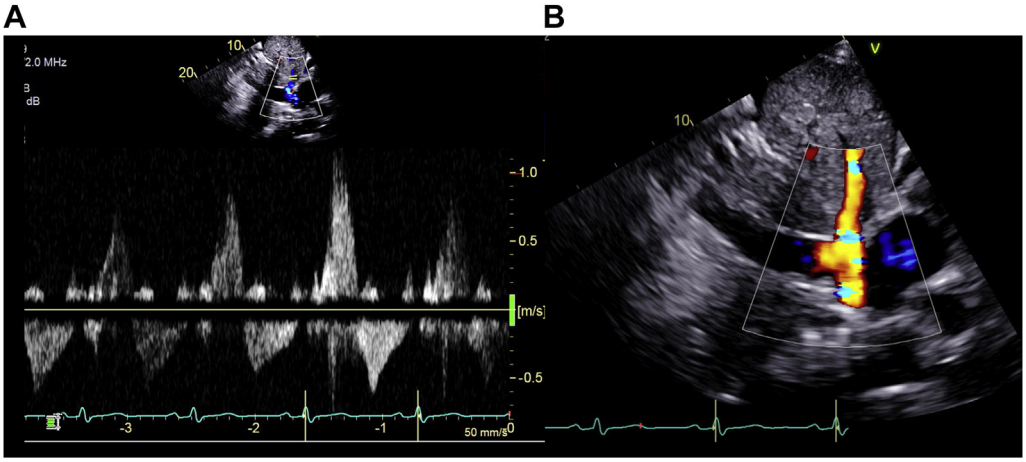

Figure 5 Two-dimensional TTE oriented in a subcostal view with pulsed-wave Doppler **(A)** and color flow Doppler **(B)** demonstrating hepatic vein systolic flow reversal consistent with severe TR.

width > 0.7 cm, proximal isovelocity surface area radius > 0.9 cm at the Nyquist limit of 30-40 cm/sec, dense/triangular continuous-wave Doppler jet or sine wave pattern, and systolic reversal of hepatic vein flow.[7] In the case of severe TR in CHD, echocardiographic findings are commonly described as a "dagger-shaped" form on continuous-wave Doppler with early peak pressures and rapid decline (Figure 2B).[4-6]

Two-dimensional TTE is the reference standard for the diagnosis of CHD and is recommended for follow-up every 3-6 months in patients with established CHD.[3,4,6] However, a multimodality imaging approach should be considered in these patients as part of a comprehensive evaluation and is often useful in perioperative planning. Additional imaging techniques, such as transesophageal echocardiography, three-dimensional echocardiography, and cardiovascular magnetic resonance imaging can better evaluate the pulmonic valve and more accurately quantify the right ventricular size and function. The presence of severe TR limits the accuracy of estimating RV systolic function by TTE (e.g., RV ejection fraction, fractional area change, tricuspid annular planar systolic excursion, and peak systolic annular velocity [S']) as these parameters overestimate RV performance with severe TR. As with severe mitral regurgitation, hyperdynamic ventricular function is required to maintain a normal forward stroke volume, and care should be taken to identify "inappropriately normal" RV functional measurements.

Three-dimensional transesophageal echocardiography and cardiovascular magnetic resonance imaging are useful alternatives to TTE in assessing RV performance as they provide volumetric stroke volume assessment.[7,8] Additional imaging is also important in CHD patients with left-sided valvular lesions, which are present in up to 15% of patients with CHD and generally less severe than right-sided

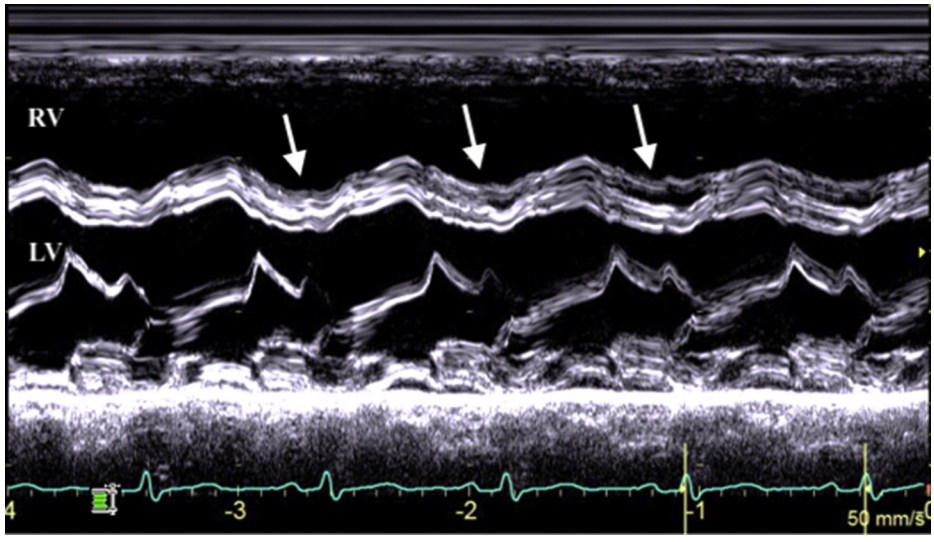

Figure 6 M-mode echocardiography oriented in a parasternal short-axis view showing diastolic septal flattening (*white arrows*) from volume overload of the RV.

Figure 7 Contrast-enhanced CT of the abdomen, coronal view, demonstrating a primary mesenteric mass (*red arrow*) and many hepatic metastases (*white arrows*).

valvular involvement.[4] When left-sided valvular lesions are present, an agitated saline contrast echocardiography should be performed to evaluate for a patent foramen ovale,[9] which allows for direct transport of 5-HT to the left side of the heart, bypassing the inactivation that occurs in the pulmonary vascular bed.[3]

As our patient continues systemic therapy for advanced CHD, he is planned to undergo a minimally invasive, endoscopic tricuspid valve replacement. Surgical management of CHD is indicated in patients with severe valvular regurgitation and well-controlled systemic disease.[3,4,9,10] Generally, patients with CHD are referred for valve replacement surgery based on the severity of their right heart failure symptoms (e.g., fatigue, dyspnea, edema, ascites) and/or evidence of right ventricular dysfunction on echocardiography.[3,4,9,10] The native valve is usually not repairable in CHD. For any patient with severe and complex valvular disease, evaluation by a multidisciplinary heart valve team is a class I recommendation.[11] However, there is a paucity of data on the optimal timing of valve replacement surgery in patients with CHD because the decision for surgical intervention is often individualized and guided by a multidisciplinary team.[3,4,9] Patients with successful valvular replacements have been found to have an improvement in symptoms and a decrease in early mortality.[3,4,9,10] Current literature supports that early surgical intervention may lead to improved outcomes[10,12-14]; further investigation in this area is needed.

The COVID-19 pandemic has transformed and reorganized many aspects of healthcare delivery. Regarding cancer care, experts have suggested potential modifications while preserving standards of care for patients with neuroendocrine neoplasia (NEN) during the COVID-19 era.[15] An example of such modification includes the utilization of telemedicine to facilitate continued multidisciplinary care and social distancing.[15] Another example is the consideration of deescalation of care, when appropriate, to minimize the risk of exposure and reduce the impact on the healthcare system.[15] Although these modifications may have little impact on slow-growing NENs and may be reasonable, these experts also strongly urge providers to make individual determinations based on the potential harms of modifying and delaying care.[15] Furthermore, care for patients with highly functional NENs (e.g., uncontrolled carcinoid syndrome and/or CHD) should be prioritized.[15] In our patient's case, he was stabilized in the hospital and nonemergent testing and imaging were deferred until after the recommended quarantine period. He then had outpatient follow-up with multidisciplinary specialists to comanage his care. As the COVID-19 pandemic continues, the healthcare community is learning together how to best care and advocate for patients during these unprecedented times.

CONCLUSION

Herein we describe the case of a middle-aged man presenting with severe TR and resultant right heart failure secondary to CHD. Although rare, CHD represents an important etiology of primary valvular dysfunction. Despite carcinoid syndrome being a well-recognized clinical entity, establishing a diagnosis and making an individualized treatment plan remain a significant challenge and require utilization of several subspecialties. Despite this patient's modified evaluation due to COVID-19, our case highlights the use of medical therapy to curb the progression of disease in addition to chemotherapy before attempting surgical intervention. While valvular replacement offers definitive therapy, the optimal timing for the intervention remains complex.

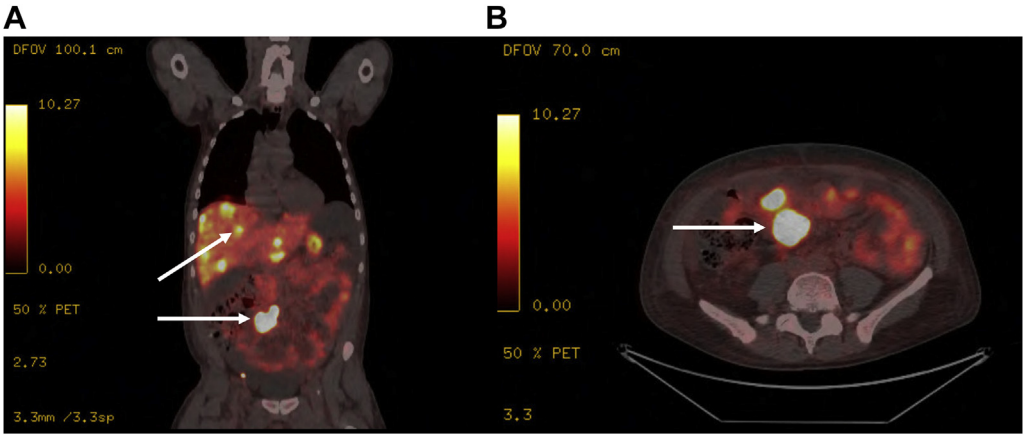

Figure 8 Gallium-68 DOTA-TATE PET/CT demonstrating increased activity within the liver, mesenteric lymph nodes, and a single lesion within the right lower quadrant (*white arrows*) in coronal **(A)** and transverse **(B)** views.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2022.01.006.

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