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CASE REPORT

BEGINNER

DAVINCI CORNER

Right and Left-Sided Carcinoid Heart Disease in the Setting of Selective Serotonin Reuptake Inhibitor Use

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ABSTRACT

Carcinoid heart disease is a complication of carcinoid syndrome. The role of selective serotonin reuptake inhibitors in carcinoid heart disease is unclear. We present a case of refractory heart failure due to right- and left-sided carcinoid heart disease in the setting of selective serotonin reuptake inhibitor use despite remission of carcinoid syndrome. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:1841–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 73-year-old female presented to the emergency department with acute heart failure. She presented afebrile with a blood pressure of 92/60 mm Hg, a heart rate of 103 beats/min, and oxygen saturation of 94% on room air. Her physical exam findings were suggestive of volume overload, including jugular venous distension, bilateral lung crackles, hepatomegaly, and lower-extremity edema.

LEARNING OBJECTIVES

- To understand the pathophysiology of carcinoid heart disease.
- To discuss the role selective serotonin reuptake inhibitors may play in the development of valvular heart disease.
- To emphasize the significant mortality associated with carcinoid heart disease.
- To discuss a potential mechanism for selective serotonin reuptake inhibitor–induced carcinoid heart disease late after carcinoid tumor therapy.

PAST MEDICAL HISTORY

Her past medical history was notable for a malignant carcinoid tumor with mesenteric metastasis in 2009, which was resected and treated with monthly octreotide injections. In June 2017, she was deemed to be in remission based on laboratory and imaging studies; therefore, octreotide was discontinued. In early 2018, she suffered multiple major depressive episodes with psychosis and was started on the selective serotonin reuptake inhibitor (SSRI) citalopram with gradual dose up-titration over the course of several months. Six months later, she developed flushing, diarrhea, and progressively worsening dyspnea on exertion requiring multiple hospitalizations.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for heart failure exacerbation included coronary ischemia, valvular heart

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ABBREVIATIONS AND ACRONYMS

5-HT = 5-hydroxytryptamine receptor

CHD = carcinoid heart disease

CS = carcinoid syndrome

NET = neuroendocrine tumor

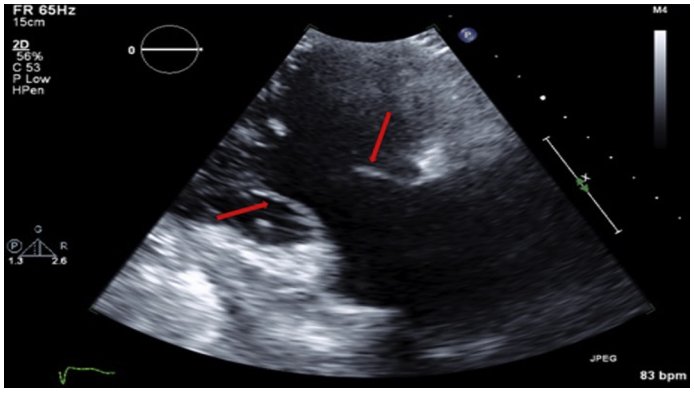
SSRI = selective serotonin reuptake inhibitor

disease, or underlying atrial or ventricular arrhythmias.

INVESTIGATIONS

Labs were remarkable for an elevated N terminal pro-B-type natriuretic peptide of 1,657 pg/ml. Chromogranin A level was markedly elevated to 1,677 ng/ml. Urine 5-hydroxyindoleacetic acid was elevated to 28.6 mg/24 h. An echocardiogram revealed a dilated left ventricle with an ejection fraction of 50%, severe tricuspid regurgitation attributed to thickened leaflets in a fixed open position (**Figure 1**), severe pulmonary regurgitation (**Figure 2**), and severe aortic regurgitation (**Figure 3**). The right ventricle was moderately dilated with moderate dysfunction. This was a marked difference from prior echocardiograms in 2015 and 2016, with an ejection fraction of 60%, trace mitral regurgitation, trace pulmonary regurgitation, no aortic insufficiency, and a structurally normal tricuspid valve. The atrial septum was intact without evidence of right-to-left shunt. Coronary angiography showed no significant coronary artery disease. An octreotide scan did not show any evidence of metastatic or recurrence of carcinoid disease. Computed tomography angiogram of the chest and abdomen did not have findings suggestive of tumor burden.

FIGURE 1 Transthoracic Echocardiography



Transthoracic echocardiography with tricuspid valve leaflets **(red arrows)** in a fixed and open position, a pathologic feature of the tricuspid valve in coronary heart disease.

MANAGEMENT

She was treated with intravenous diuresis then transitioned to oral torsemide before discharge. Octreotide therapy was reinitiated. No additional medications were started. She was discharged home to await surgical replacement of the tricuspid and aortic valve.

DISCUSSION

Neuroendocrine tumors (NETs) mainly arise from exocrine cells throughout the gastrointestinal tract and to a lesser extent, the bronchopulmonary system, releasing vasoactive amines, such as prostaglandins, bradykinin, histamine, and most prominently, serotonin (5-hydroxytryptamine receptor [5-HT]) (1). These tumor products are usually inactivated by the liver. However, with metastases to the liver, hormonal activity may exceed the hepatic capacity for degradation leading to carcinoid syndrome (CS) (1). Symptoms are characterized by cutaneous flushing, gastrointestinal hyper-motility, and bronchospasm (2). The cardiac manifestations of an NET are referred to as carcinoid heart disease (CHD), also called Hedinger syndrome. Carcinoid tumors are rare with 27 per 1,000,000 diagnosed in the United States per year according to the National Organization of Rare Diseases. Only 10% of NETs develop CS (1). Once CS is established, more than half of these patients will go on to have carcinoid tumors specifically involving the heart (2,3). The tricuspid valve is most commonly affected, whereas the pulmonic valve is involved 60% of the time. Left-sided valves are rarely impacted and account for <10% of cases due to the pulmonary metabolism and deactivation of the hormonal substances (4,5). Left-sided involvement usually occurs in either the presence of right-to-left shunt, carcinoid of the lung, or very high levels of vasoactive substances (2). The development of cardiac pathology in a patient with CS has a 3-year survival rate of 31%, whereas patients without cardiac involvement have approximately twice the survival rate (2,3). The burden of illness can be significant for patients living with NET, and they often experience depression and anxiety requiring treatment with SSRIs. Whether SSRIs are safe to use in combination with treatment for NET remains controversial.

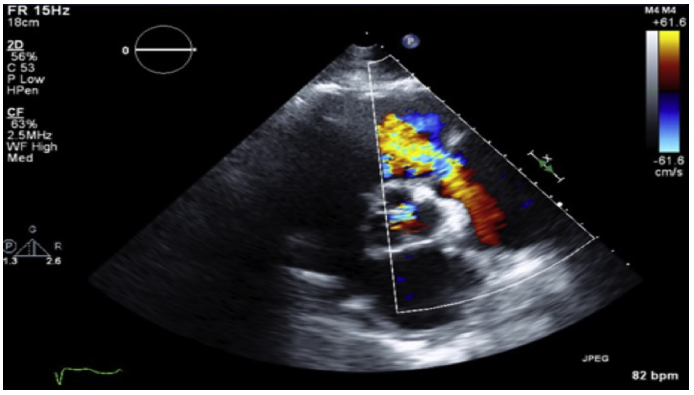
The exact mechanism for development of CHD in the setting of CS is poorly understood. A strong body of evidence implying that 5-HT is linked to cardiac

valve disease exists (3,5-7). The popular diet pill fenfluramine-phentermine, which has 5-HT-releasing activity from the 5-HT transporter, brought to light the relationship between 5-HT and valvular heart disease (8). Remarkably, the valve pathology seen with the use of fenfluramine-phentermine is similar to findings in CHD. 5-HT_{2B}, a subtype of the 5-HT receptor, is most prevalent on cardiac valves (4-6,9). Activation of 5-HT_{2B} causes upregulation of fibroblast proliferative properties, such as tissue growth factor B1, which leads to deposition of plaques on the endocardial surfaces of the valve leaflets and the subvalvular apparatus (3-5,7); thus, resulting in valve regurgitation. Urinary 5-hydroxyindoleacetic acid, the serotonin metabolite which reflects the amount of serotonin production, is significantly higher in patients with CHD compared with those without cardiac involvement (2,10), implicating 5-HT as the mechanism for valvular heart disease. SSRIs increase the availability of 5-HT by inhibiting the 5-HT transporter that transports 5-HT from synaptic spaces into presynaptic neurons (9). Somatostatin receptors are expressed in approximately 80% to 90% of NETs, which makes them a therapeutic target (8). The mechanisms by which somatostatin and its analogues exert their effects on the NET cells are complex and not well described (8). We know from various studies that use of somatostatin analogues can modify the 3-dimensional configuration of somatostatin receptors. This alteration affects receptor regulation and density at the cell surface (8), which may explain why somatostatin analogue resistance is encountered in patients with CS after long-term octreotide therapy. We theorize a similar modification may occur with 5-HT receptors after long-term use of octreotide. Although no evidence establishes the role of SSRIs in CHD, multiple case reports regard SSRIs as responsible for unmasking CS in patients with an occult carcinoid tumor (9).

FOLLOW-UP

Her surgery was initially postponed due a continuing rise in chromogranin A level despite octreotide therapy. She was transitioned to lanreotide as this has been shown to have similar efficacy and is better tolerated than octreotide. Telotristat ethyl, a tryptophan hydroxylase inhibitor that reduces peripheral 5-HT levels, was also initiated. Because of the coronavirus disease 2019 pandemic, her surgery has been postponed.

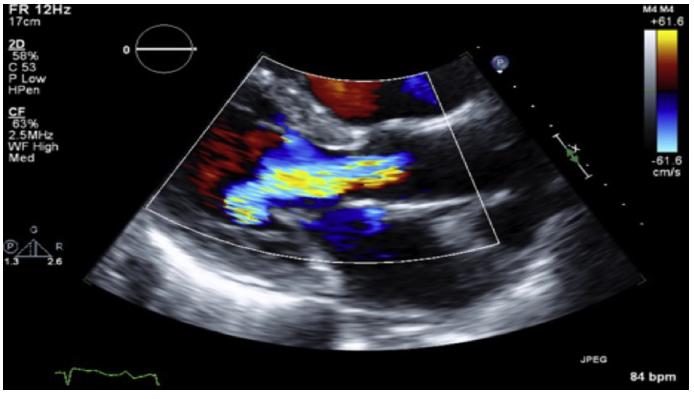
FIGURE 2 Severe Pulmonary Regurgitation With Free Regurgitant Flow



CONCLUSIONS

Guidance on the safety of antidepressants in NETs, CS, and CHD is lacking. To our knowledge this is the first case report where SSRIs may cause rapid progression of CS to CHD in the setting of previous treatment with a somatostatin analogue. We hypothesize that the exposure to long-term octreotide changes the density and/or sensitivity of 5-HT receptors on carcinoid tumors, laying the foundation for a predisposition to CHD. Coupled with the additional insult of increased 5-HT availability from SSRIs, a reactivation of CS occurred with subsequent CHD. Unmasking of undetectable micro-disease by the use of SSRIs cannot be excluded. This case highlights the

FIGURE 3 Severe Aortic Regurgitation



Rare carcinoid involvement of the aortic valve.

potential provocative role SSRIs play in the rapid progression of right- and left-sided CHD. CHD portends a worse prognosis and represents a major cause of morbidity and mortality. Death as a result of cardiac decompensation in this patient population is as high as 43% in untreated patients (3). Therefore, this possible association between SSRIs and CHD is important to consider when managing patients with depression and a history of CS.

AUTHOR RELATIONSHIP WITH INDUSTRY

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Aluri V, Dillon JS. Biochemical testing in neuroendocrine tumors. Endocrinol Metab Clin North Am 2017;46:669–77.

2. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart 2004;90:1224–8.

3. Rajamannan NM, Caplice N, Anthikad F, et al. Cell proliferation in carcinoid valve disease: a mechanism for serotonin effects. J Heart Valve Dis 2001;10:827–31.

4. Jian B, Xu J, Connolly J, et al. Serotonin-induced up-regulation of transforming growth factor-β1 via G-protein signal transduction in aortic valve interstitial cells. Am J Pathol 2002; 161:2111–21.

5. Simbera Z, Balon R. Carcinoid tumor, selective serotonin reuptake inhibitors, and diarrhea. Psychosomatics 2005;46:88–9.

6. Elangbam CS, Job LE, Zadrozny LM, et al. (2008) 5-Hydroxytryptamine (5HT)-induced valvulopathy: compositional valvular alterations are associated with 5HT2B receptor and 5HT transporter transcript changes in Sprague-Dawley rats. Exp Toxicol Pathol 2008;60:253–62.

7. Connolly JM, Bakay MA, Fulmer JT, et al. Fenfluramine disrupts the mitral valve interstitial cell response to serotonin. Am J Pathol 2009;175: 988–97.

8. Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer 2008;15:701–20.

9. Williams MD, Dolenc TJ. Selective serotonin reuptake inhibitors and patients with carcinoid tumor. Psychosomatics 2005;46:370–2.

10. Zuetenhorst JM, Bonfrer JM, Korse CM, Bakker R, van Tinteren H, Taal BG. Carcinoid heart disease: the role of urinary 5-hydroxyindoleacetic acid excretion and plasma levels of atrial natriuretic peptide, transforming growth factor-β and fibroblast growth factor. Cancer 2003;97:1609–15.

KEY WORDS carcinoid heart disease, carcinoid syndrome, Hedinger syndrome, valvular disease