

Case report

Balancing carcinoid crisis and right ventricular dysfunction during tricuspid and pulmonic valve replacement for carcinoid heart disease: A case report[☆]

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ABSTRACT

Introduction and importance: Carcinoid tumors are rare malignancies of neuroendocrine origin that can manifest with a constellation of systemic symptoms including right-sided cardiac involvement. Many patients with carcinoid heart disease require valve replacement, but intraoperative management of carcinoid syndrome varies within the literature.

Case presentation: A 72-year-old man with carcinoid syndrome underwent tricuspid and pulmonic valve replacement with multiple episodes of carcinoid crisis intraoperatively as well as right ventricular dysfunction after cardiopulmonary bypass.

Clinical discussion: Octreotide is the mainstay in prevention and treatment of intraoperative carcinoid crisis, but reported dosages and timing varies significantly. The use of exogenous catecholamines is also controversial as they are thought to paradoxically worsen carcinoid symptoms. Our patient was managed successfully with both an octreotide infusion and intermittent boluses, as well as exogenous catecholamines for right ventricular support during and after cardiopulmonary bypass.

Conclusion: The management of carcinoid syndrome in patients undergoing valve surgery for carcinoid heart disease is dependent on timely prevention and treatment of carcinoid crisis and effective mitigation of right ventricular dysfunction.

1. Introduction

Carcinoid tumors are rare malignancies originating from gastrointestinal or bronchopulmonary neuroendocrine cells [1,2]. When disease bypasses hepatic metabolism, bioactive peptides produced by these tumors affect the systemic circulation and cause symptoms collectively termed carcinoid syndrome [2]. Cutaneous flushing, bowel hypermotility, vasodilation with hypotension, bronchoconstriction, and right-sided valvular heart disease are characteristic features of carcinoid syndrome [2,3]. Left heart valves are usually spared unless a right-to-left shunt, a bronchopulmonary primary tumor, or a lung metastasis is

present [3].

Anesthetic management of patients with carcinoid syndrome during cardiac surgery involves preventing cardiovascular instability from release of vasoactive substances (carcinoid crisis) and managing hemodynamic derangements resulting from tricuspid or pulmonary valve replacement and cardiopulmonary bypass to mitigate right ventricular dysfunction [4,5]. The use of vasoactive drugs is counterintuitive to conventional thinking because these medications may exacerbate release of vasoactive peptides from the tumor.

We describe a patient with carcinoid syndrome who underwent tricuspid and pulmonic valve replacement during which intraoperative

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carcinoid crises were managed with octreotide and right ventricular function was supported using vasoactive medications. This report is written in accordance with the SCARE criteria [6].

2. Presentation of case

A 72-year-old man presented to our institution with facial flushing, diarrhea, fatigue, dyspnea on exertion, and weight loss of 3 years' duration with worsening over 6 months. The patient's medical history was notable for hypertension, hyperlipidemia, and type 2 diabetes mellitus, with no history of tobacco or alcohol abuse. The physical examination revealed a systolic murmur best heard at the left sternal border, as well as grade 2 pitting edema in the lower extremities. A laboratory analysis was notable for an elevated level of 5-hydroxyindoleacetic acid (208 $\mu\text{mol}/24\text{ h}$, normal range 10–47 $\mu\text{mol}/24\text{ h}$). Computed tomography and Gallium-68 positron emission tomography demonstrated a small bowel tumor with mesenteric, omental, and liver metastases (Figs. 1, 2). A biopsy of a hepatic metastasis was consistent with a well-differentiated carcinoid tumor (Fig. 3). Subcutaneous lanreotide injections were prescribed (120 mg every 4 weeks; subsequently increased to 180 mg). Transesophageal echocardiography (TEE) mid-esophageal 4-chamber and transgastric right ventricular inflow views revealed severely restricted motion of the tricuspid valve leaflets and severe regurgitation (Figs. 4, 5, and 6; video clips 1, 2, and 3). A mid-esophageal right ventricular inflow-outflow TEE view also showed pulmonic valve leaflet immobility and severe insufficiency (Fig. 7, video clip 4). The right ventricle was dilated, but its systolic function was grossly normal. Coronary angiography showed moderate-severe disease in the left anterior descending artery as well as severe disease in the first obtuse marginal artery. The patient was taken to the operating room for coronary revascularization and tricuspid and pulmonic valve replacement.

An octreotide infusion (50 $\mu\text{g}/\text{h}$) was initiated 1 h before surgery. During surgery, several episodes of refractory hypotension with facial flushing were observed consistent with carcinoid crisis. Escalating bolus doses of phenylephrine, epinephrine, and vasopressin failed to restore normal arterial pressure, but bolus doses of octreotide (5 to 10 μg) rapidly resolved the hypotension. The continuous infusion of octreotide was increased to 200 $\mu\text{g}/\text{h}$, after which no further episodes of carcinoid crisis were observed. The native tricuspid and pulmonic valves were excised and replaced with 29 mm and 23 mm bioprostheses, respectively. Coronary revascularization was not feasible because distal vessels

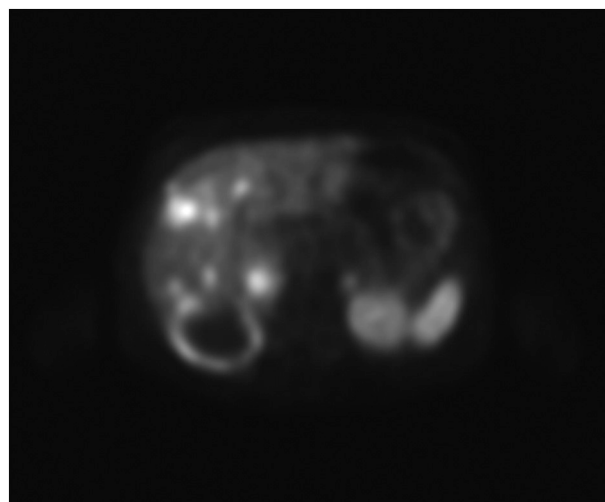


Fig. 2. Positron emission tomography scan confirming hepatic metastases.

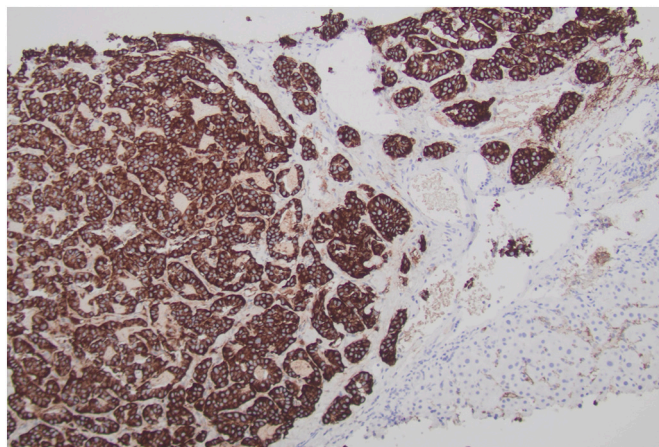


Fig. 3. Hematoxylin and eosin histological slide of a liver biopsy with chromogranin staining, revealing neuroendocrine tumor on the left of the slide and normal liver on the right.

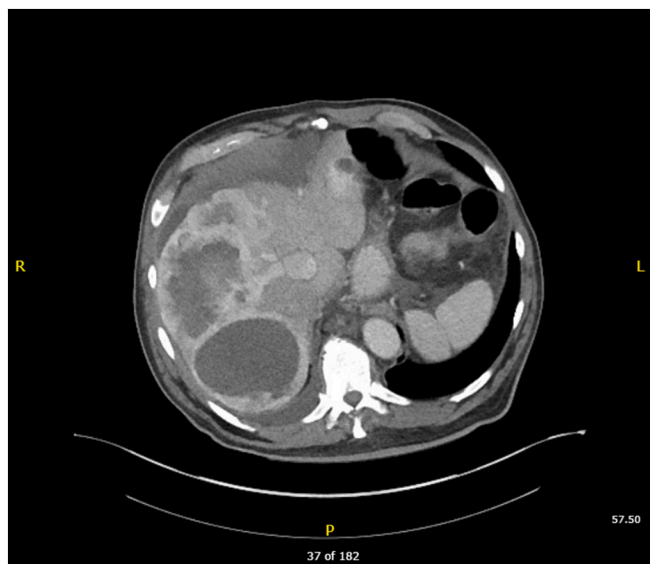


Fig. 1. Computed tomography scan revealing extensive hepatic metastases.

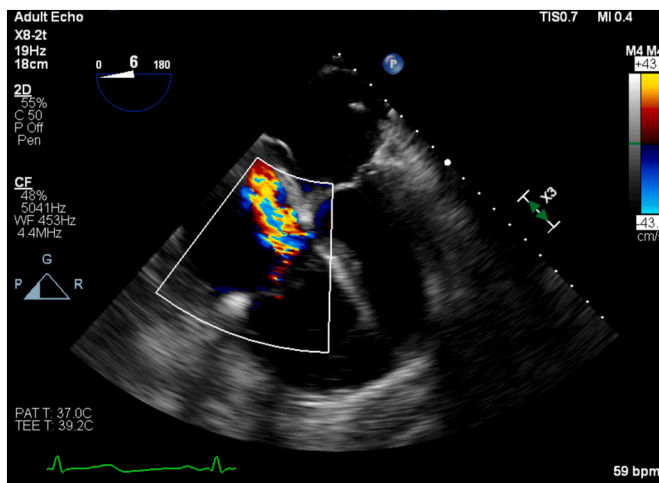


Fig. 4. Midesophageal 4-chamber color Doppler TEE view demonstrating severe tricuspid regurgitation.

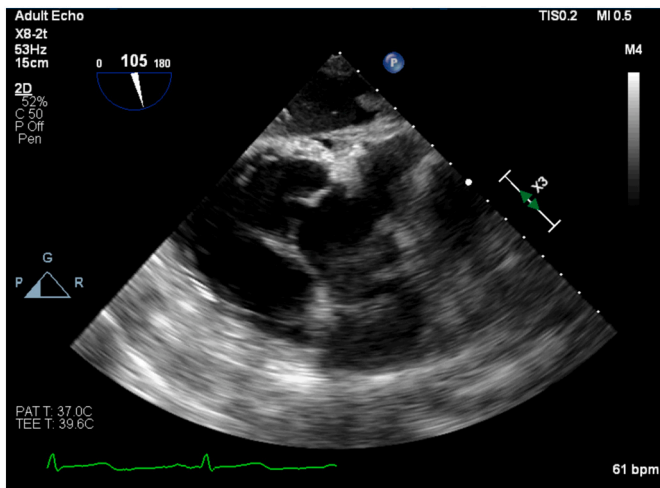


Fig. 5. Transgastric right ventricular inflow TEE view demonstrating thickening, calcification, and immobility of the tricuspid leaflets.

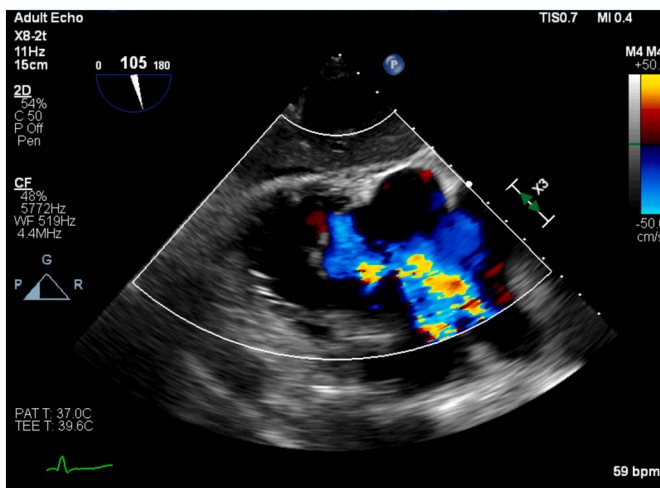


Fig. 6. Transgastric right ventricular inflow color Doppler TEE view demonstrating severe tricuspid regurgitation.

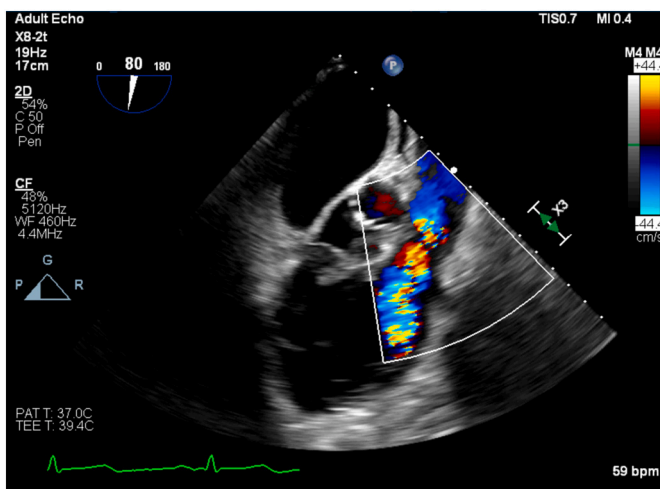


Fig. 7. Midesophageal right ventricular inflow-outflow color Doppler TEE view showing severe pulmonic insufficiency.

were of insufficient caliber. The patient's heart was weaned from bypass using inotropic support (milrinone, norepinephrine, and epinephrine) and inhaled nitric oxide (40 ppm). Vasopressin was added for refractory vasoplegia. The patient was transferred to the intensive care unit with the octreotide infusion maintained at 100 $\mu\text{g}/\text{h}$. He was subsequently weaned from mechanical ventilation and his trachea was extubated on the first postoperative day. Both the octreotide infusion and vasoactive drug support were discontinued on the second postoperative day. The patient was discharged on the seventh postoperative day without complication. The patient has since shown progression of disease with episodes of small bowel obstruction and is on peptide receptor radionuclide therapy.

3. Discussion

The incidence of carcinoid tumor is approximately 1 in 75,000. Approximately 10 to 50 % patients develop carcinoid syndrome, of which one-half to two-thirds develop valvular involvement because of endocardial deposition of plaque-like fibrous tissue [5]. Carcinoid heart disease manifests preferentially on right-sided valves because downstream metabolism of vasoactive products by the lung occurs [3,7]. Left-sided valve disease can occur in the presence of intracardiac shunts or when metastatic disease overcomes the lungs' ability to metabolize bioactive peptides [2]. Valve repair or replacement has been shown to improve symptoms and prolong survival in patients with carcinoid heart disease [2,3,8–11].

Carcinoid tumors produce and release several distinct bioactive peptides including serotonin, histamine, kinins, insulin, catecholamines, and prostaglandins [4]. Serotonin is the most important pathophysiological mediator of symptoms and disease progression [2,5]. The precise mechanism(s) by which serotonin causes valve injury is still unclear, but the relationship between serotonin and cardiac involvement may be mediated by upregulation of transforming growth factor- β and collagen synthesis by myofibroblasts in the extracellular matrix [2,4,9,12,13]. Deposition of fibrous plaques within the tricuspid and pulmonic valve leaflets, subvalvular apparatus, right ventricular endocardium, and large vessels (e.g. vena cavae, pulmonary artery) are observed [3,7]. Tricuspid regurgitation via a Carpentier type IIIA mechanism is most frequently seen as fibrous deposition usually develops on the right ventricular surface of the valve, resulting in dilation of the right ventricle and tricuspid annulus [2,14]. The pulmonic valve usually displays stenosis and regurgitation when it is affected, as fibrin deposition on the arterial side of the valve may cause valve leaflet fusion with the pulmonary vascular endothelium [7,14,15]. Both valve lesions contribute to eventual right ventricular dysfunction [1,2]. Valve replacement often worsens preexisting right ventricular dysfunction perioperatively by eliminating the low-pressure outlet [2,5]. Myocardial stunning resulting from inadequate myocardial protection during cardiopulmonary bypass further exacerbates this phenomenon [1,2,5,16]. In our patient, inotropic support and inhaled nitric oxide were required to support right ventricular function during and after separation from bypass.

Carcinoid crisis is characterized by acute hemodynamic instability associated with flushing and bronchoconstriction, caused by release of vasoactive substances from neuroendocrine cells secondary to triggers such as anxiety, sympathetic nervous system stimulation, medication-induced histamine release, tumor manipulation, and hypothermia [1,2,7,4,17]. The mainstay of prevention and management of carcinoid crisis is octreotide, a somatostatin analog that inhibits vasoactive substance release [2,5]. The literature has reported highly variable dosing recommendations to guide the use of octreotide [1,2,4,7,17]. Published retrospective case series or observational studies are difficult to interpret because of inconsistent findings, small sample size, and the lack of a uniform definition for carcinoid crisis [2,4,18,19]. Nevertheless, published recommendations and institutional protocols continue to advocate for the use of octreotide despite the lack of robust evidence

supporting its efficacy, arguing that its potential beneficial effects outweigh the risks [2,4]. A typical octreotide regimen incorporates a 50 to 100 µg/h infusion begun 12 h before major surgery, which is continued for 48 h with additional dose escalations or boluses for symptom control [1,2,4,7,9,17]. We followed this approach in our patient, but we began the octreotide infusion only 1 h before surgery. Our patient's outpatient treatment with subcutaneous lanreotide influenced our decision because his most recent dose was administered 5 days before surgery. Our use of bolus octreotide administered for intraoperative carcinoid crisis also differed from previous reports. Many authors described using bolus doses of 50 to 100 µg, but our patient needed only 5 to 10 µg boluses in combination with an octreotide infusion to 200 µg/h to stabilize hemodynamics. Octreotide may be ineffective in preventing or treating carcinoid crisis, as some studies describe development of tachyphylaxis to the drug [11,18].

Synthesis and release of vasoactive substances from carcinoid tumor cells may be precipitated by administration of catecholamines and cause a paradoxical reaction when vasoactive medications are used to treat hypotension [1,2,7]. Nevertheless, catecholamines are not expressly contraindicated in carcinoid syndrome [1,2,4,7]. Indeed, the data supporting the avoidance of catecholamines is lacking [20]. Castillo et al. recommended initial treatment of hypotension in carcinoid syndrome with octreotide and volume resuscitation, but they also acknowledged that vasoactive medications may have efficacy in combination with octreotide [2]. Limbach et al. conducted a large retrospective review of carcinoid patients undergoing elective abdominal procedures during which carcinoid crises were treated with or without β-agonists. There were no differences in the magnitude or duration of carcinoid crises between the two groups, and postoperative outcomes were similar [20]. Our patient did not exhibit more pronounced hypotension during administration of vasoactive medications. Indeed, phenylephrine, norepinephrine, vasopressin, and epinephrine were used to manage right ventricular dysfunction and systemic hypotension that were unrelated to carcinoid crisis. Our patient would have been unable to separate from bypass without vasoactive drug support including β-agonists.

4. Conclusion

In summary, we describe our management of a complex patient with carcinoid heart disease undergoing tricuspid and pulmonic valve replacement. Carcinoid crises were treated with escalating doses of octreotide and vasopressors, and right ventricular dysfunction was managed with inotropic medications during separation from cardiopulmonary bypass with no paradoxical reactions to exogenous catecholamines.

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Ethical approval

Ethical approval is exempt/waived at our institution.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Research registration

N/A.

Guarantor

Dustin Hang, MD.

CRediT authorship contribution statement

Adam R. Pagryzinski: Conceptualization, Writing – original draft, Resources. **Stefano Schena:** Resources, Writing – review & editing. **Jutta Novalija:** Resources, Writing – review & editing. **G. Hossein Almassi:** Resources, Writing – review & editing. **Paul S. Pagel:** Conceptualization, Writing – review & editing, Visualization, Supervision. **Dustin Hang:** Conceptualization, Writing – original draft, Writing – review & editing, Resources, Visualization, Supervision.

Declaration of competing interest

None.

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