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Use of perioperative telotristat in a patient with carcinoid heart disease

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Summary

Carcinoid heart disease is a rare complication of carcinoid syndrome, resulting in right-sided valvular heart disease and subsequent heart failure due to long-term exposure to vasoactive substances. The management of this condition is complex, often requiring surgical intervention. Current perioperative regimens entail the use of prophylactic somatostatin analogs to prevent carcinoid crisis; however, regimens vary widely among practitioners and evidence supporting their efficacy in this clinical setting is mixed. This case report describes the perioperative management of a 65-year-old man with carcinoid heart disease requiring tricuspid and pulmonary valve replacement surgery. As an adjunct to somatostatin analog therapy, the novel tyrosine hydroxylase inhibitor, telotristat, was initiated preoperatively. This combination resulted in normalization of preoperative urinary 5-HIAA levels. The patient successfully underwent tricuspid and pulmonic valve replacement without evidence of carcinoid crisis. This clinical case is the first published documenting the use of telotristat in the perioperative period in a patient with carcinoid syndrome and carcinoid heart disease and was associated with a good long-term outcome despite the high-risk nature of the case.

Learning points

- Carcinoid crisis is a life-threatening complication of carcinoid syndrome, resulting in hemodynamic instability, bronchospasm, and arrhythmia.
- Cardiac surgical patients with carcinoid syndrome present a unique challenge as they are subject to physiologic conditions and medications which can potentiate intraoperative carcinoid crisis.
- Perioperative management of patients with carcinoid syndrome currently entails the use of prophylactic somatostatin analogs; however, these agents do not prevent carcinoid crisis in all cases.
- Telotristat, a tryptophan hydroxylase inhibitor, shows promise as an adjunctive therapy to somatostatin analogs to reduce the risk of intraoperative carcinoid crisis.

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Background

Carcinoid syndrome (CS) affects patients with neuroendocrine tumors (NET) due to the release of vasoactive substances including serotonin. Common clinical manifestations include cutaneous flushing, diarrhea, and bronchospasm (1, 2). Long-term complications may occur as a consequence of prolonged exposure to high concentrations of vasoactive substances, such as carcinoid heart disease and mesenteric fibrosis (3). Carcinoid crisis (CC) is a life-threatening complication that can occur in patients with CS. The proposed pathophysiology is attributed to the sudden release of vasoactive substances resulting in hemodynamic instability, bronchospasm, and arrhythmia (3).

Carcinoid heart disease (CHD) is a complication of CS. It commonly presents as right-sided valvular fibrosis (secondary to serotonin-mediated cardiac fibroblast stimulation) with right-sided heart failure (1). It occurs in 20–50% of patients diagnosed with CS (1, 2). The management of CHD is challenging and requires a multidisciplinary approach (1). Medical therapies can be employed to optimize cardiac function and control hormone hypersecretion; however, patients with severe symptomatic CHD may ultimately require surgical valve replacement (2). Right ventricular dysfunction commonly coexists with tricuspid and pulmonary regurgitation in these patients, leading to increased operative risk (6). Cardiac surgical patients present a unique challenge as they are subject to physiologic conditions and medications which can potentiate carcinoid crisis, making preoperative optimization essential (2). Preoperative and perioperative use of somatostatin analogs (SSAs) to control hypersecretion of 5-HIAA and other vasoactive substances is the standard of care to prevent intraoperative CC, which is associated with increased risk of major postoperative complications (2, 4). Though protocols vary, this typically involves initiation of a long- and/or short-acting SSA preoperatively and octreotide infusion intraoperatively (2, 4). However, the reported efficacy of pre- and intra-operative SSAs in preventing CC is variable, and they do not prevent CC in all cases (4). Failure to achieve control of serotonin levels with SSAs preoperatively may be a contributing factor; therefore, novel adjuvant therapies for CS deserve consideration (4).

Telotristat is an oral inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the peripheral conversion of tryptophan to serotonin. Telotristat is approved for the management of CS, including refractory CS associated diarrhea. This agent has potential for use as adjuvant therapy in preoperative management of CS to prevent perioperative CC. Currently, there is no literature reporting on the use of telotristat in this setting. This case report describes a patient with CS that underwent cardiac surgery for management of CHD and received adjuvant therapy with telotristat perioperatively.

Case presentation

A 65-year-old man was diagnosed with metastatic grade 1 neuroendocrine tumor in September 2021. He reported symptoms of weight loss, diarrhea, weakness, and abdominal discomfort and was found to have multifocal hepatic lesions occupying 75% of the hepatic parenchyma (largest lesion 8.9 × 7.4 × 5.2 cm) on triphasic CT (Fig. 1). A bilobed avidly enhancing lesion was also visualized within the wall of a right lower quadrant ileal segment, which was suspected to represent the primary tumor. Ultrasound-guided biopsy of one of the hepatic lesions was performed, and pathology was consistent with a metastatic well-differentiated grade 1 neuroendocrine tumor (Ki-67 <3%). CDX2 and SATB2 staining were suggestive of a gastrointestinal primary. Biochemistry showed elevated chromogranin A (662 ng/mL) and 24-h urinary 5-HIAA (602 µmol/day) (Table 1). His clinical course was complicated by CHD detected shortly after diagnosis, presenting primarily as right heart failure with anasarca and New York Heart Association (NYHA) IV dyspnea. He did not have any symptoms suggestive of intestinal obstruction.

Investigation

Transthoracic and transesophageal echocardiograms revealed torrential tricuspid regurgitation, thickened pulmonic valve with moderate pulmonary regurgitation, moderately reduced right ventricular systolic function, and severe right ventricle dilation (Figs. 2 and 3).

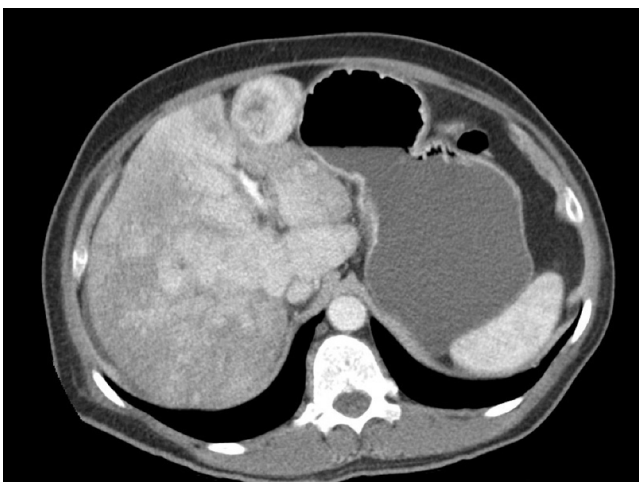

Figure 1

Axial section from venous phase of triple-phase CT scan demonstrating unresectable hepatic metastases.

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Table 1 Biochemical values throughout treatment course.

			1 month post initiation of		
	Reference range	**Baseline** (August 2021)	SSA (December 2021)	Telotristat (January 2022)	10 months post-op (October 2022)
24-h urine 5-HIAA, µmol/day	10–40	602	468	28	11
Chromogranin A, ng/mL	<110	662	–	–	–
ALT, U/L	<59	28	32	88	15
ALP, U/L	40–120	738	649	361	202
GGT, U/L	<79	212	339	189	103
Total bilirubin, µmol/L	0–24	27	15	7	3

ALP, alkaline phosphatase; ALT, alanine transferase; GGT, gamma glutamyl transferase; 5-HIAA, 5-hydroxyindoleacetic acid.

He had an elevated N-terminal pro-brain-type natriuretic peptide (NT-proBNP) of 2017 ng/L (ref: <900 ng/L). Right heart catheterization demonstrated mean right atrial pressure 14 with v-wave to 26, pulmonary artery systolic pressure 26, and pulmonary artery diastolic pressure 14. There was equalization of pulmonary artery and right ventricular pressures in mid-diastole consistent with severe pulmonary regurgitation.

Treatment

Given the patient's cardiac status, management of his carcinoid heart disease was prioritized. The patient was admitted to hospital in November 2021 under the cardiology service for medical optimization prior to valve replacement surgery. In addition to diuretics, therapy was initiated with SSA (initially short-acting subcutaneous octreotide with subsequent transition to lanreotide LAR 120 mg every 28 days), which reduced but did not normalize 5-HIAA levels (Table 1). Approximately 4 weeks prior to surgery, telotristat 250 mg t.i.d. was initiated as an adjunctive therapy with aim to normalize 5-HIAA levels and reduce the risk of perioperative CC. The patient did not meet diarrheal criteria for telotristat; however, this agent was initiated based on recommendation from multidisciplinary NET tumor board to medically optimize the patient preoperatively given the high risk nature of this case and persistent elevation in 5-HIAA levels. The patient underwent tricuspid (31 mm St Jude Epic bioprosthetic, Abbott Laboratories, Abbott Park, IL, USA) and pulmonary (size medium Perceval sutureless bioprosthetic, Corcym UK, London, UK) valve replacement with right ventricular outflow tract reconstruction via pericardial patch. SSA and telotristat were continued perioperatively. Intraoperative management included 1000 µg bolus of octreotide during anesthesia induction, followed by 1.409 µg/kg/h octreotide infusion, which was in accordance with the planned protocol from preoperative anesthesia

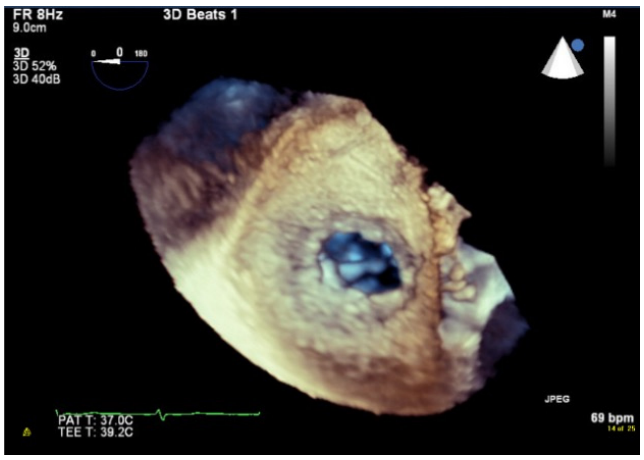

Figure 2

Three-dimensional transesophageal echo image of the tricuspid valve from an atrial view. There is carcinoid disease of the tricuspid valve – with severe circumferential thickening of the annulus, leaflets and subvalvular apparatus.

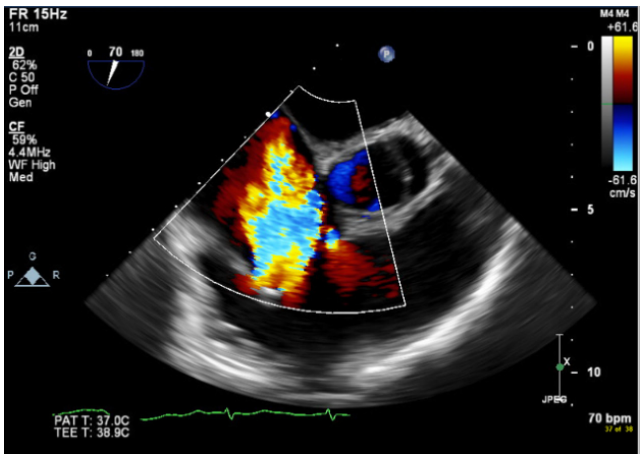

Figure 3

Mid-esophageal short-axis view at the aortic valve level. Color Doppler demonstrates torrential tricuspid regurgitation related to restricted leaflet motion.

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consultation. The octreotide infusion rate was reduced to 0.704 µg/kg/h approximately 3 h into the operation, and no further boluses of octreotide were required.

Outcome and follow-up

The procedure was successful, without any intraoperative complications and no evidence of CC intra- or post operatively. The patient was transferred to the cardiovascular intensive care unit in stable condition. On postoperative day 4, the patient developed progressive abdominal pain, distension, and hypotension and was found to have ischemic bowel with perforation, necessitating laparotomy with small bowel resection. Intraoperatively he was found to have an ischemic section of the jejunum measuring approximately 30 cm, which was associated with jejunal diverticular disease. There was suspicion that this could have been caused by the small bowel primary well-differentiated neuroendocrine tumor; however, this was not evident on surgical pathology. His postoperative course was otherwise uneventful, and he was discharged home 14 days after cardiac surgery. Since discharge, the patient has been maintained on lanreotide and telotristat with no symptoms of CS and maintenance of normal 24 h urinary 5-HIAA levels. Cross-sectional imaging performed at 4, 10, and 14 months postoperatively did not show any evidence of disease progression.

Discussion

CHD is a known complication of CS. It is mediated through long-term exposure to high serum concentrations of vasoactive substances, such as serotonin, prostaglandins, and tachykinins. This affects cardiac 5-HT2B receptors, resulting in serotonin-mediated stimulation of cardiac myocytes and fibroblasts with resultant fibrotic plaque development (2, 3). Pulmonary and tricuspid valve insufficiency with right-sided heart failure is the most common manifestation of CHD. The incidence of left heart involvement is rare, occurring in the context of significantly elevated concentrations of vasoactive substances overwhelming pulmonary degradation capacity, primary bronchopulmonary carcinoid disease, or intracardiac shunts (1, 2). CHD may initially present as nonspecific dyspnea and fatigue and progress to right-sided heart failure with edema, pleural effusions, and ascites (3). Echocardiography is the mainstay for diagnosis of CHD and often demonstrates thickened right-sided heart valves and associated valvular insufficiency (1, 3).

Surgical intervention is indicated for definitive management of CHD, particularly in cases with symptomatic valvular disease or right ventricular dysfunction (2). Surgical management of CHD is considered high risk, with historical estimates of 18% mortality attributed primarily to tumor-related complications (7). This is particularly critical given the high operative risk associated with right-sided valve operations in patients with right ventricular dysfunction (6). CC is a vital consideration for patients with CS undergoing surgical intervention, due to the risk of hemodynamic instability and subsequent perioperative complications, including death. Avoidance of sympathetic stimulation and histamine releasing medications (e.g. morphine) are common considerations for anesthesia but are insufficient to prevent CC alone (5). Although vasopressors and inotropes have been used successfully without CC, they are still considered potential triggers for perioperative CC (5). CHD cardiac surgical patients frequently have right ventricular systolic dysfunction, which obligates the use of vasopressors and inotropes, in addition to the sympathetic responses to surgical stress, putting them at risk of CC. Furthermore, postoperative hypotension, which is common after cardiac surgery as a result of vasoplegia or low systemic vascular resistance states, is very difficult to distinguish from CC, and escalation of vasopressor therapy has the potential to worsen or cause CC. Preoperative mediator suppression is essential to reduce overall perioperative risk. Perioperative management of patients with CS currently entails the use of prophylactic SSAs, which aim to reduce excessive hormone production and symptoms related to CS (5). However, the data supporting the efficacy of SSAs for prevention of perioperative CC are mixed (4, 5, 8). A meta-analysis evaluated the incidence of CC in cases of well-differentiated NET across eight studies involving 943 operations (primarily abdominal) found that the use of prophylactic SSAs was not associated with reduced risk of CC (4). The potential morbidity of CC, paired with the paucity of high-quality clinical data to support current practices, prompts the evaluation of adjunctive strategies to prevent CC perioperatively.

Telotristat is currently approved for the treatment of CS associated diarrhea as an adjunct to somatostatin analogs for refractory symptoms, and has been shown to significantly reduce 24-h urine 5-HIAA levels, carcinoid associated symptoms, and improve quality of life (9, 10). Two pivotal phase III clinical trials, TELESTAR and TELECAST, investigated the efficacy and safety of telotristat. The TELESTAR trial demonstrated clinical efficacy via a statically significant reduction in the number of daily bowel movements, reduction in urine 5-HIAA levels, and improvement of quality of life scores, with further support for safety and efficacy demonstrated in the TELECAST trial (9, 10). Inadequate control of 5-HIAA levels preoperatively has been postulated to contribute to the variable efficacy of SSAs in preventing CC; therefore, telotristat represents an attractive adjunctive therapy in this setting (4). However, the impact of telotristat in the prevention of perioperative CC has not been previously evaluated. This report documents a case of perioperative

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management using SSAs and adjuvant telotristat in a patient with CS and CHD. The addition of telotristat to SSAs resulted in normalization of urinary 5-HIAA levels and was well tolerated by the patient without any adverse effects. Importantly, normalization of urinary 5-HIAA occurred within 4 weeks of telotristat initiation, which we presume is secondary to both initiation of telotristat and ongoing SSA effect. The rapid normalization of 5-HIAA was critical in this case as the patient was not expected to tolerate a long wait for surgery due to poor cardiac function. Despite a large hepatic tumor burden, markedly elevated baseline 5-HIAA levels, and significant RV dysfunction, CC did not occur. Furthermore, the patient tolerated a second operation without incident and has had excellent postoperative and long-term outcomes. CC is a rare clinical phenomenon, and the role of serotonin in CC have not been completely established. Furthermore, specific data from cardiac surgery are limited. As such, we cannot ascertain a causative relationship between the lack of CC and the initiation of telotristat based upon a single case report. This case illustrates the impact on a potential mechanism of CC, namely, lowering of markedly elevated 5-HIAA level preoperatively, and highlights the need for further investigation into the use of telotristat as an adjunctive agent in this setting.

Declaration of interest

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the case study reported.

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Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient and a relative of the patient.

Author contribution statement

All authors contributed to the conception, writing, and revision of the manuscript. KL, RM, JP and CN evaluated and managed the patient preoperatively. CA performed valve replacement surgery and CN performed anesthesia.

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