

CASE REPORT

An unusual cause of hypoxia: getting to the heart of the matter

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Summary

A 63-year-old female presented to hospital with progressive exertional dyspnoea over a 6-month period. In the year preceding her admission, she reported an intercurrent history of abdominal pain, diarrhoea and weight loss. She was found to be hypoxic, the cause for which was initially unclear. A ventilation-perfusion scan identified a right-to-left shunt. Transoesophageal echocardiography (TOE) demonstrated a significant right-to-left intracardiac shunt through a patent foramen ovale (PFO); additionally severe tricuspid regurgitation was noted through a highly abnormal tricuspid valve. The findings were consistent with carcinoid heart disease with a haemodynamically significant shunt, resulting in profound systemic hypoxia. 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) and imaging were consistent with a terminal ileal primary carcinoid cancer with hepatic metastasis. Liver biopsy confirmed a tissue diagnosis. The patient was commenced on medical therapy for carcinoid syndrome. She subsequently passed away while undergoing anaesthetic induction for valvular surgery to treat her carcinoid heart disease and PFO.

Key Words

- ▶ carcinoid syndrome
- ▶ patent foramen ovale
- ▶ shunt

Learning points:

- Carcinoid syndrome is a rare condition, which presents a significant diagnostic challenge due to its insidious presentation and symptoms. This frequently results in a marked delay in diagnosis.
- Carcinoid heart disease is characterised by distortion and fixation of right-sided heart valves, which cause valvular regurgitation, stenosis or both. Valvular abnormalities are often found in association with right ventricular failure.
- In the case described, carcinoid heart disease was found in association with a significant right-to-left intracardiac shunt, created through a PFO due to right atrial volume overload. This prevented right ventricular failure at the expense of creating a state of severe induced systemic hypoxia.
- This physiological adaptation resulted in an unusual presentation of this condition, due to symptoms resulting from hypoxia, rather than the classical symptoms of carcinoid syndrome or right ventricular failure.

Background

Exertional breathlessness is a common presenting complaint in acute medicine. Hypoxia is a common clinical finding in these patients. This case demonstrates an unusual cause of hypoxia. Standard first-line investigations would not have reached the underlying diagnosis in this case and as such it demonstrates the complex investigative strategy required to reach this diagnosis. The case illustrates the challenges of diagnosing carcinoid syndrome. It was only through investigation of the exertional breathlessness that the underlying diagnosis of carcinoid syndrome with carcinoid heart disease was made.

Case presentation

A 63-year-old female presented acutely to hospital with progressive dyspnoea over the previous 6 months. She had no other significant medical co-morbidities, but 2 months previously had been investigated for chronic lower abdominal pain, weight loss and diarrhoea, which had started 1 year beforehand. Recent outpatient investigations into her gastrointestinal symptoms, including a pelvic ultrasound scan and a colonoscopy, had been unremarkable and consequently these symptoms had been attributed to irritable bowel syndrome.

On admission to hospital, she was cachectic with a body mass index (BMI) of 19. Observations identified resting hypoxia, with oxygen saturation of 91% on room air; other observations were within normal parameters. Cardiovascular examination revealed a pansystolic murmur at the left sternal edge, there was no peripheral oedema and her venous jugular pressure was not elevated. Respiratory system examination was unremarkable with no peripheral or central cyanosis and vesicular breath sounds bilaterally throughout the lung fields.

Investigation

Arterial blood gas on room air confirmed type I respiratory failure with pO_2 7.64 kPa. Blood tests (including full blood count, renal function, liver function and C-reactive protein) were all unremarkable. 12-lead electrocardiogram showed normal sinus rhythm with a normal cardiac axis. Chest radiograph was unremarkable and did not identify any parenchymal, interstitial or pleural abnormalities that could account for the hypoxia.

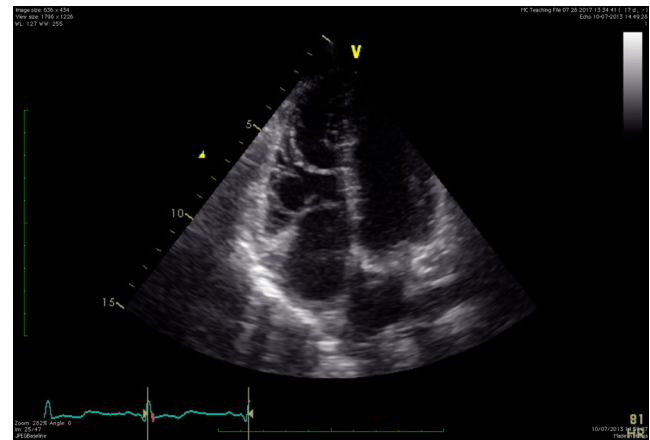


Figure 1
TTE apical 4-chamber view, demonstrating abnormal tricuspid valve appearance.

A computed tomography (CT) pulmonary angiogram demonstrated no evidence of a pulmonary embolism, but an ill-defined hypodense lesion in the liver was noted that was suspicious for a metastatic deposit. Persistent hypoxia was further investigated with a ventilation-perfusion (VQ) nuclear scan, which showed no evidence of perfusion defect to suggest thromboembolic disease, but did confirm the presence of a large right-to-left shunt.

Echocardiography was performed to assess for the presence of an intracardiac shunt. Transthoracic echocardiography (TTE) was limited by suboptimal windows, but identified an abnormal tricuspid valve appearance with restriction and splinting of the valve leaflets with loss of coaptation causing severe regurgitation and mild stenosis (Figs 1, 2 and Video 1). Right ventricular

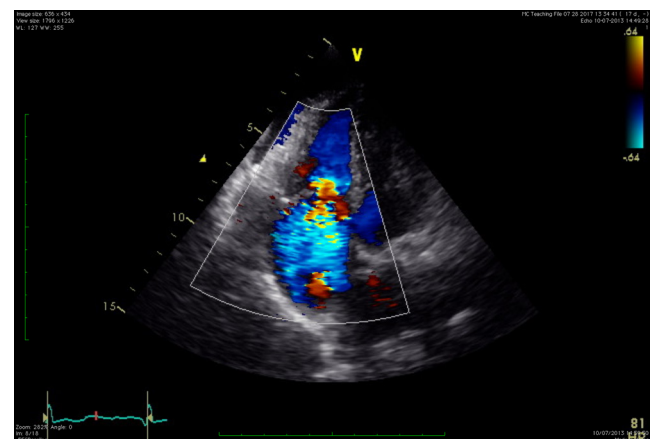


Figure 2
Colour Doppler showing severe tricuspid regurgitation.

Video 1

TTE apical 4-chamber view, demonstrating restriction and splinting of the tricuspid valve leaflets. View Video 1 at <http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0055/video-1>.

Video 2

TOE mid-oesophageal aortic valve short axis view, demonstrating highly mobile aneurysmal 'skipping rope' interatrial septum. View Video 2 at <http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0055/video-2>.

Video 3

TTE bubble saline contrast injection demonstrating significant right-to-left shunt. View Video 3 at <http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0055/video-3>.

Video 4

TOE bubble saline contrast injection demonstrating significant right-to-left shunt. View Video 4 at <http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0055/video-4>.

dimensions (Fig. 3) and systolic function were within normal limits (Fig. 4).

Transoesophageal echocardiography (TOE) demonstrated a highly mobile aneurysmal 'skipping rope' interatrial septum (Video 2). Colour Doppler confirmed flow across the interatrial septum (Fig. 5). Bubble saline contrast injection identified a significant right-to-left shunt through a PFO (Videos 3 and 4). Aortic and mitral valves were mildly thickened and only mildly regurgitant. The mechanism of the shunt was therefore identified

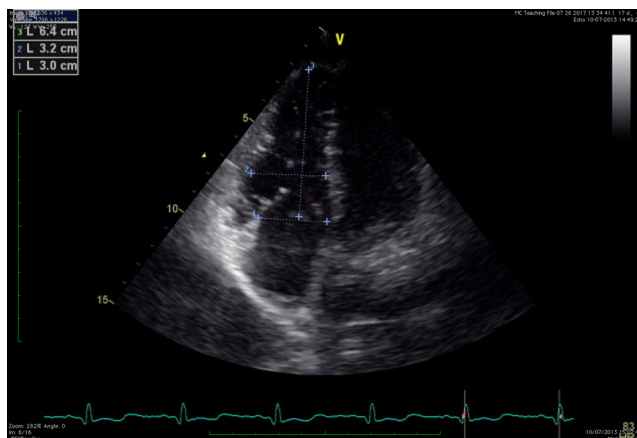


Figure 3
TTE apical 4-chamber view demonstrating normal right ventricular dimensions.

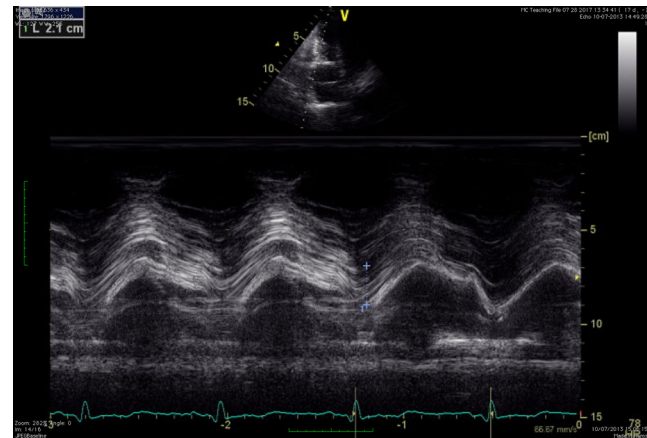


Figure 4
M-mode demonstrating normal RV systolic function, as indicated by TAPSE 2.1 cm.

as an acquired intracardiac circuit occurring as a result of a severely regurgitant tricuspid valve with the jet of regurgitation being directed across a PFO into the left atrium due to right atrial volume overload.

In view of the patient's symptoms of weight loss, abdominal pain and diarrhoea, 24-h urinary collection for 5-hydroxyindoleacetic acid (5-HIAA) was performed. This was significantly elevated at 717 $\mu\text{mol}/24\text{h}$ (normal range $<42\mu\text{mol}/24\text{h}$) and therefore strongly suggestive of carcinoid syndrome as the underlying pathology. Serum chromogranin A and B levels were elevated. A CT abdomen and pelvis identified a 1 cm hypervascular lesion in the terminal ileum in addition to mesenteric lymphadenopathy and a hypervascular hepatic lesion, in keeping with a primary carcinoid lesion with hepatic metastasis. MRI liver confirmed an 8 cm right liver lobe

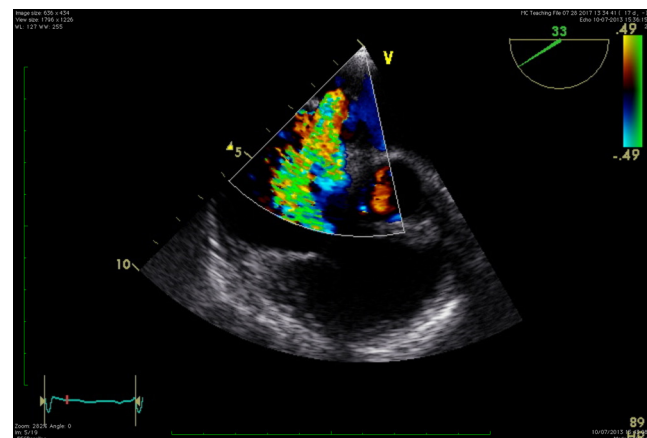


Figure 5
TOE mid-oesophageal aortic valve short axis view with colour Doppler, demonstrating significant flow across the interatrial septum.

mass. Octreotide scan confirmed a solitary hepatic deposit with further uptake in the terminal ileum. Percutaneous biopsy of the liver lesion confirmed a well-differentiated metastatic carcinoid tumour.

Treatment and outcome

Sandostatin, an analogue of the hypothalamic release-inhibiting hormone somatostatin, was commenced which resulted in temporary relief of gastrointestinal symptoms. The patient's care was transferred to a tertiary centre experienced in the management of carcinoid syndrome and carcinoid heart disease (CHD). A multi-disciplinary decision was taken to proceed to valvular surgery with PFO closure. During induction for the operation, the patient developed severe hypotension with fulminant circulatory collapse and died before surgery could be undertaken.

Discussion

Carcinoid syndrome is a clinical manifestation of a well-differentiated neuroendocrine tumour (NET). The NET arises from enterochromaffin cells, located in either the gastrointestinal tract or the lungs, which are responsible for the release of vasoactive substances such as serotonin. Carcinoid syndrome usually occurs in patients with metastatic lesions to the liver, which results in failure of hepatic inactivation of the vasoactive substances or their release directly into the systemic circulation. The characteristic symptoms are diarrhoea, cutaneous flushing and bronchoconstriction. Carcinoid tumours are rare, with an estimated incidence of 1–2 per 100,000 in the United States of America (1, 2).

Carcinoid syndrome can present a diagnostic challenge to physicians, due to its indolent presentation, in association with an unusual constellation of symptoms. The typical time from onset of symptoms to diagnosis is 24–28 months, but is sometimes as long as 5 years (3). Diagnosis can be reached using a combination of 24-h HIAA urinary excretion levels, blood tests for 5-HIAA and chromogranin and imaging modalities. Imaging techniques used include CT, MRI, OctreoScan scintigraphy and positron emission tomography integrated with CT (PET CT). Biopsies allow tissue diagnosis and confirm the degree of differentiation of the tumour.

CHD is a known complication of carcinoid syndrome. It is estimated to occur in over 50% of patients with this condition (4). The pathophysiology is via a paraneoplastic effect of the

high levels of secreted vasoactive substances on the right heart, without inactivation of these substances by the liver. This results in fibrous plaque deposition and endocardial thickening, which can cause retraction, distortion and fixation of the right-sided heart valves. This results in valvular regurgitation, stenosis or both. The vasoactive substances are degraded within the lungs, therefore, relatively protecting the left heart from the disease (3, 4).

Patients with CHD typically present with signs of severe tricuspid regurgitation and right heart failure in association with classical systemic carcinoid syndrome symptoms. Valvular surgery is the only definitive treatment of CHD, with prosthetic valvular replacement usually preferred when patients are considered suitable operative candidates (3). Other strategies address symptom control though treatment of right ventricular failure with diuretics. Somatostatin analogues can relieve carcinoid symptoms and slow tumour growth (5).

In the case described, the patient had symptoms of carcinoid syndrome with echocardiographic evidence of CHD. However, in spite of severe tricuspid valvular disease, there were no clinical features of right heart failure due to the unique haemodynamic adaptation created by the shunt. The right heart was effectively offloading through the PFO, causing a right-to-left shunt. Although this had prevented fulminant features of right heart failure, this came at the expense of an induced state of profound hypoxia created by the shunt. As such, this is a unique presentation of this condition as it came to light from symptoms relating to the hypoxia, rather than those typically described in this condition.

PFO, in its own right, is a common phenomenon, present in 25% of the population. It is usually benign and not associated with a significant shunt as left atrial pressure is higher than right atrial pressure in the physiologically normal heart (6). In the case described, the torrential tricuspid regurgitation caused by CHD resulted in raised right atrial pressure; this in turn caused the continuous right-to-left shunt across the PFO creating a haemodynamically significant lesion. A single small study has identified a higher incidence of significant PFO in patients with CHD compared with age-matched controls and suggests that in some cases there may be a role for percutaneous closure of haemodynamically significant lesions (7). Symptoms of platypnea–orthodeoxia syndrome have been reported in patients with a PFO and an additional predisposing feature, which results in significant shunting of blood from the right atrium to left atrium (8). Although physiologically feasible in the case described, the symptoms of this syndrome were not specifically described by the patient.

The presence of a PFO in a patient with carcinoid syndrome also creates a conduit for passage of the vasoactive substances released in carcinoid syndrome from the right heart to the left heart. This can, in theory, result in the involvement of left-sided heart valves in addition to the right-sided heart valves and has been described elsewhere in the literature (9).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Patient consent

The patient is deceased. Written consent for publication of the submitted article and accompanying images and videos has been given from the patient's next-of-kin.

Author contribution statement

D H and A S drafted the manuscript and contributed equally as first author. M M Z contributed to the manuscript. P B was involved in the patient's care and reviewed the manuscript. L S was involved in the patient's care and reviewed the manuscript.

References

- 1 Møller JE, Connolly HM, Rubin J, Seward JB, Modesto K & Pellikka PA. Factors associated with progression of carcinoid heart disease. *New England Journal of Medicine* 2003 **348** 1005–1015. (<https://doi.org/10.1056/nejmoa021451>)
- 2 Bertin N, Favretto S, Pelizzo F, Mos L, Pertoldi F & Vriz O. Carcinoid heart disease: starting from heart failure. *Journal of Investigative Medicine High Impact Case Reports* 2017 **5** 2324709617713511. (<https://doi.org/10.1177/2324709617713511>)
- 3 Fox DJ & Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. *Heart* 2004 **90** 1224–1228. (<https://doi.org/10.1136/hrt.2004.040329>)
- 4 Connolly HM & Pellikka PA. Carcinoid heart disease. *Current Cardiology Reports* 2006 **8** 96–101. (<https://doi.org/10.1007/s11886-006-0019-9>)
- 5 Van der Lely AJ & de Herder WW. Carcinoid syndrome: diagnosis and medical management. *Arquivos Brasileiros de Endocrinologia and Metabologia* 2005 **49** 850–860. (<https://doi.org/10.1590/s0004-27302005000500028>)
- 6 Hagen PT, Scholz DG & Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clinic Proceedings* 1984 **59** 17–20. ([https://doi.org/10.1016/S0025-6196\(12\)60336-X](https://doi.org/10.1016/S0025-6196(12)60336-X))
- 7 Mansencal N, Mitry E, Pillière R, Lepère C, Gérardin B, Petit J, Gandjbakhch I, Rougier P & Dubourg O. Prevalence of patent foramen ovale and usefulness of percutaneous closure device in carcinoid heart disease. *American Journal of Cardiology* 2008 **101** 1035–1038. (<https://doi.org/10.1016/j.amjcard.2007.11.056>)
- 8 Alkhouli M, Gagel A, Mathur M & O'Murchu B. Platypnea-orthodeoxia syndrome: an unusual complication of partial liver resection. *Internal Medicine* 2015 **54** 1067–1069. (<https://doi.org/10.2169/internalmedicine.54.3617>)
- 9 Connolly HM, Schaff HV, Mullany CJ, Rubin J, Abel MD & Pellikka PA. Surgical management of left-sided carcinoid heart disease. *Circulation* 2001 **104** I36–I40. (<https://doi.org/10.1161/hc37t1.094898>)

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