

Metastatic small bowel neuroendocrine tumour and carcinoid heart disease with aortic valve involvement – a rare occurrence

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Abstract: Carcinoid disease of the heart commonly affects the tricuspid and pulmonary valves causing thickening and stenosis. However in very rare circumstances, the disease can also involve the mitral and aortic valves. We present an unusual case of left sided carcinoid heart disease (CHD) and triple valve replacement without the presence of proven intra-cardiac shunts or bronchial carcinoid lesions.

Keywords: Carcinoid heart disease (CHD); aortic valve; mitral valve; 5-hydroxytryptamine

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Introduction

Neuroendocrine tumours are rare gastrointestinal tumours of the enterochromaffin origin. Malignant carcinoid syndrome can result in 20–30% of patients, who can present with flushing, hypotension, diarrhoea, and bronchospasm (1). This is often due to the release of vasoactive substances such as 5-hydroxytryptamine (serotonin), 5-hydroxytryptophan, histamine, bradykinins, tachykinins, and prostaglandins (2).

Carcinoid heart disease (CHD) as an entity, involves fibrous plaque deposition on the endocardial surface of the cardiac valves and chambers, which occurs in up to 70% of patients with carcinoid syndrome (3). The exact mechanism behind CHD is still unknown; however prolonged exposure to elevated levels of serotonin and vasoactive mediators has been theorised as a possible mechanism.

Case presentation

We report a case of a 66-year-old male who originally presented with abdominal pain, anaemia and a positive fecal occult blood test. Computed tomography of the abdomen and pelvis confirmed an obstructive mass of the transverse colon as well as multiple cystic lesions of the liver. He proceeded to have an extended right hemicolectomy with the pathological specimen indicative of stage IIA low-

grade adenocarcinoma. A staging positron emission scan (PET) demonstrated multiple gallium dotatate avid foci in the liver and adjacent small bowel mesentery. Fine needle biopsies of the liver indicated low grade neuroendocrine carcinoma. Clinically, the patient described episodic coughing and diarrhea, which along with the liver histology established a diagnosis of carcinoid syndrome. At the time of diagnosis, baseline tests were performed including chest X. rays, electrocardiograms, echocardiograms. With an established diagnosis, serum Chromogranin A (CgA) level was monitored to assess disease progression and response to therapy. The patient's CgA level was initially found to be 233.8 nmol/L (reference range <3.0 nmol/L), which eventually dropped to 50–85 nmol/L on monthly medical treatment with a somatostatin analogue, Lanreotide acetate (Somatuline® Autogel®, Ipsen Pty Ltd., Australia) which helps relieve symptoms from carcinoid syndrome and slow progression of neuroendocrine tumors.

Several years into his treatment, the patient presented hospital on multiple occasions with symptoms of right heart failure and episodes of atrial arrhythmias. Initial transthoracic echocardiogram at the time of diagnosis showed mildly thickened tricuspid valve leaflets with severe tricuspid regurgitation (*Figure 1A,B*) and mild aortic, pulmonic and mitral regurgitation. This has rapidly progressed to biventricular failure as subsequent

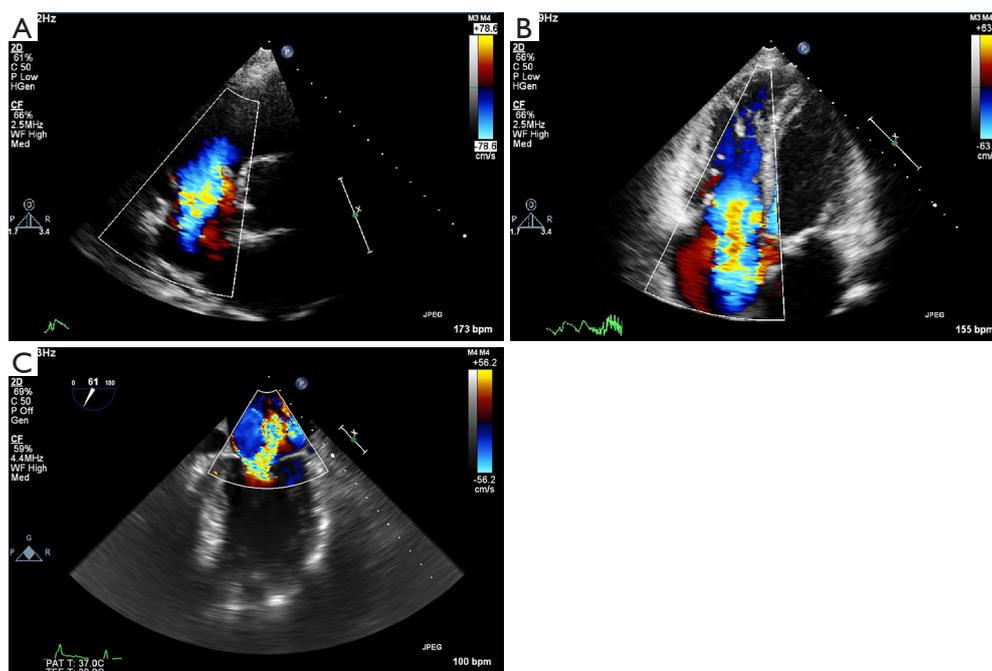


Figure 1 Echocardiogram images demonstrating valvular changes associated with CHD. (A) Transthoracic echo-severe tricuspid valve regurgitation; (B) transthoracic echo-apical 4 chamber view-severe tricuspid valve regurgitation; (C) transesophageal echocardiogram-mitral valve regurgitation. CHD, carcinoid heart disease.

transesophageal echocardiogram confirmed changes of left and right sided CHD: a tricuspid valve with severe regurgitation, failed coaptation of the non-coronary, left-coronary aortic valve leaflets with severe regurgitation; pulmonary valve thickening and moderate pulmonic regurgitation; moderate mitral regurgitation (Figure 1C) and biatrial dilatation. Consequently, the patient was referred for surgical management of his valvular CHD. Preoperative angiogram demonstrated evidence of single vessel coronary artery disease with a 50% lesion in the left anterior descending artery while left ventriculogram showed normal contraction and end-diastolic pressures.

The patient underwent elective triple valve replacement and coronary artery bypass surgery via a median sternotomy and full cardiopulmonary bypass using aorto-bicaval cannulation.

The aortic, pulmonary and tricuspid valves were replaced with bioprosthetic tissue valves. Post operatively, the patient's recovery in hospital was uneventful, and he was discharged home on day 7 as per our department's usual post-operative algorithm. On follow-up, the patient's symptoms of heart failure have absolved, and the patient's CgA levels continued to remain stable.

The histology of the resected valves confirmed chronic carcinoid valvulopathy. The valve leaflets were stained with Masson blue, Verhoeff-van Gieson (VVG) and Alcian Blue Periodic acid Schiff (APBAS) stains. The sections (Figures 2,3) demonstrated nodular deposits of hyalinised fibrous tissue, interspersed with occasional areas of myofibroblastic proliferation and deposition of myxoid ground substance with patchy chronic inflammation and neovascularisation. This histological change was more pronounced in the tricuspid valve. There was no suggestion of metastatic neuroendocrine tumours involving the cardiac valves.

Discussion

Neuroendocrine tumours are rare tumours that arise from enterochromaffin cells. Circulating serotonin levels have been found to be higher in patients with CHD compared to carcinoid patients without any cardiac involvement (3). One theory is that prolonged exposure to elevated levels of serotonin may play a vital role in the development of CHD. Serotonin-mediated upregulation of TGF- β 1 with stimulated collagen synthesis by interstitial heart valve cells is thought to contribute to the process of leaflet fibrosis and retraction (4).

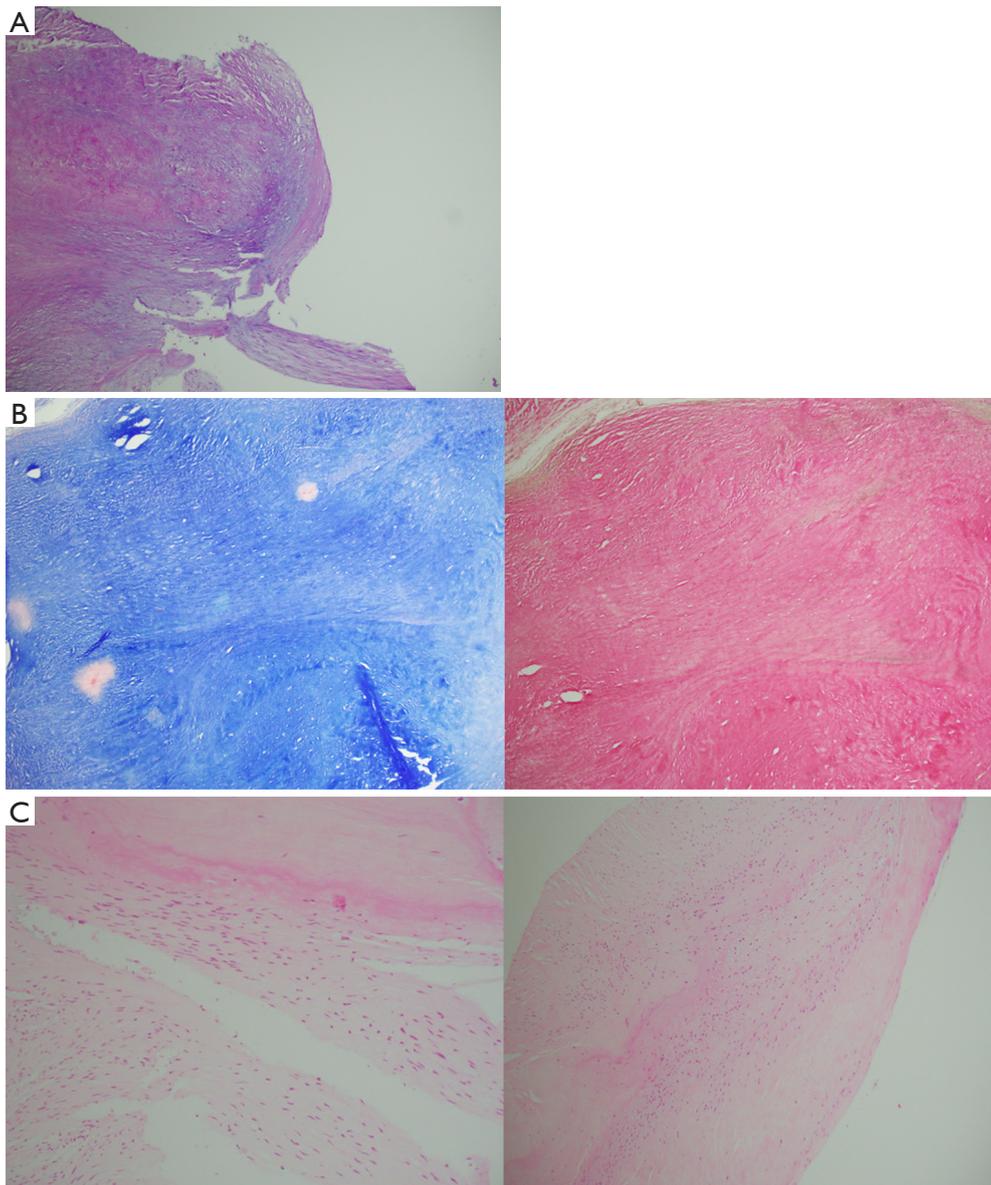


Figure 2 Histopathology of the excised aortic valve with typical carcinoid changes. (A) Aortic valve stained with APBAS demonstrating myxoid deposition (10× magnification); (B) aortic valve stained with Masson blue and VVG demonstrating hyalinised fibrous connective tissue (10× magnification); (C) aortic valve demonstrating myofibroblastic proliferation (40× and 10× magnification). APBAS, Alcian Blue Periodic acid Schiff; VVG, Verhoeff-van Gieson.

Progress in the management of malignant carcinoid tumours and carcinoid syndrome has resulted in improved patient outcomes. Somatostatin analogues have been shown to inhibit the secretion of vasoactive substances, thereby relieving symptoms in greater than 70% of patients (5).

Nevertheless, CHD patients often have high morbidity and mortality. CHD commonly affects the right heart

valves in 85% of cases and the left heart valves in less than 15% of instances (2). Valves of the right heart circulation are more commonly affected as serotonin is inactivated by monoamine oxidase to non-vasoactive 5-hydroxyindoleacetic acid (5-HIAA) in the lungs; thereby sparing the left-sided heart valves. Some reports have described that the mitral and aortic valves can be affected

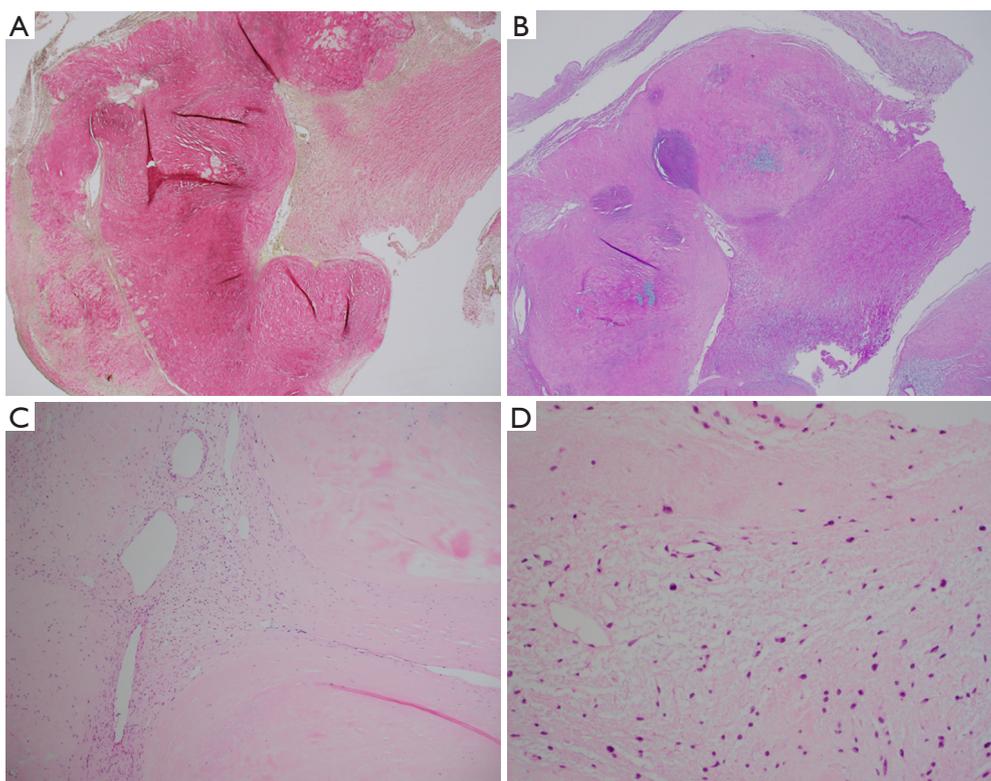


Figure 3 Chronic carcinoid valvulopathy which is more pronounced in the tricuspid valve. (A) Tricuspid valve stained with VVG demonstrating fibrous connective tissue (10× magnification); (B) tricuspid valve stained with APBAS demonstrating myxoid deposition (10× magnification); (C) tricuspid valve stained with VVG demonstrating fibrous connective tissue (10× magnification); (D) tricuspid valve demonstrating myofibroblastic proliferation (40× magnification). APBAS, Alcian Blue Periodic acid Schiff; VVG, Verhoeff-van Gieson.

in the presence of bronchial carcinoid lesions, intra-cardiac shunts such as a patent foramen ovale or membranous atrial septal defects. In this instance, the patient had mild aortic and mitral regurgitation which rapidly deteriorated without the presence of documented intra-cardiac shunts, presenting with multiple hospital admissions for episodes of atrial tachyarrhythmias and progressive congestive heart failure. It is possible that disorganised contractility, turbulence within the atrium or pre-existing left sided valvular disease contributed to the accumulation of vasoactive substances within the left sided heart chambers leading up to CHD in this case.

Definitive valve replacement surgery is indicated for patients who have progressive congestive cardiac failure despite optimal medical management. Surgery for CHD is relatively high risk. One case series reported a 30-day mortality of 18% due to perioperative complications, such as right ventricular heart failure, renal dysfunction,

sepsis and carcinoid crisis (6). However, long term survival following surgery has demonstrated significantly improved New York Heart Association functional status and 1- and 2-year survival rates of 56% and 44% respectively (6).

Conclusions

This is a rare instance of left sided CHD in context of elevated levels of CgA despite maximal medical treatment. This case highlights the occurrence of CHD in the absence of proven intra-cardiac shunts and bronchial carcinoid lesions. Mechanisms of increased levels of vasoactive substances within the left sided cardiac chambers are still not well established, but this finding affirms the need for close surveillance of patients with carcinoid disease. Early diagnosis and management of carcinoid valve disease could potentially improve prognosis and long term functional

status for the patient.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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