Vigilance for carcinoid heart disease is still required in the era of somatostatin analogues: Lessons from a case series

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Short title: Carcinoid heart disease despite SSAs

Key words: Carcinoid heart disease; somatostatin analogues; octreotide; echocardiogram; screening

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Abstract

Aim: Carcinoid heart disease (CHD) is a well-documented complication of neuroendocrine tumours (NETs) due to secreted hormones causing fibrosis. Somatostatin analogues (SSAs) can decrease hormonal secretion and inhibit tumour growth. The reported incidence of CHD has decreased as SSA
use has increased. We describe a series of patients who have developed CHD even though they were treated with SSA therapy.

Methods: Nine patients were seen in four centres in Australia and New Zealand. The average duration of follow-up from diagnosis was 39 months.

Results: Three patients had Grade 1 and six Grade 2 disease by World Health Organisation 2010 criteria. All patients had no CHD symptoms at baseline and started SSA therapy soon after diagnosis, yet developed significant, symptomatic cardiac dysfunction in their disease course. The median time from NET diagnosis to SSA initiation was 1 month, and median time from NET diagnosis to CHD diagnosis was 23 months (range 4-52). All patients who were tested had persistently increased hormonal levels (Chromogranin A, urinary 5-hydroxyindolacetic acid).

Conclusions: The good symptomatic control afforded by SSAs should not lead to reduced vigilance in screening for CHD, especially in patients with persistently elevated hormonal assays. Clinicians should consider regular echocardiographic screening in patients with a secretory syndrome.

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Introduction

Neuroendocrine tumours (NETs) are uncommon tumours, most often located in the midgut, pancreas and lung. NETs demonstrate great variability in aggressiveness and clinical course, but the complication of valvular heart disease portends a poor prognosis. Carcinoid heart disease (CHD) - valvular heart disease as a complication of NETs - was first noted by Thorson et al\(^1\) and confirmed by Bean\(^2\) who reported two patients dying from right sided heart failure. CHD has become a recognised complication of NETs, and historically occurred in up to 50% of patients with carcinoid syndrome\(^3\).
The pathogenesis of carcinoid heart disease is mediated by the release of vasoactive hormones, particularly serotonin as well as neuropeptide K and substance P. The effects of serotonin are mediated through multiple pathways, including the stimulation of phospholipase C and phospholipase A2, upregulation of nitric oxide synthase, and increased local secretion of inflammatory cytokines. The administration of serotonin in animal models led to deposition of fibrotic plaques in cardiac valves and endomyocardium, leading to valvular dysfunction. Right-sided cardiac involvement is more common, likely from the presence of hepatic metastases and hence reduced inactivation of these substances in the liver. Left-sided involvement may occur in severe cases with high tumour burden (e.g. multiple liver metastases) or a patent foramen ovale resulting in bypass of the portal circulation. Whilst bronchial primaries have historically been associated with left-sided disease, recently published evidence suggests that this may not be the case.

CHD is diagnosed based on clinical findings in combination with cardiac imaging. Transthoracic echocardiogram (TTE) remains the gold standard investigation and is also useful in quantifying severity of CHD. Technical guidelines exist for the performance of TTE in the surveillance of NETs, but the ESMO guidelines are still somewhat vague on screening procedures and their frequency in patients with functional NETs who have no cardiac symptoms. One recently published expert consensus guideline suggested that all patients with increased pro-B-type Natriuretic Peptide (pro-BNP) and/or 24-hour urinary 5-hydroxyindolacetic acid (u5HIAA) levels should be screened by TTE.

Plasma biomarkers such as pro-BNP have been recommended by some societies for CHD screening at baseline, based on two large single-institution studies, although this is not routinely recommended in all guidelines.

Early identification of CHD is critical due to its potential irreversibility, inexorable progression and the significant impact on patient survival relative to disease progression. A landmark paper reported on the characteristics of CHD by screening 132 NET patients and showed that overall survival at 3 years was poorer for patients with CHD at 31% compared to 68% for those without CHD. Prognosis is
particularly poor in patients with New York Heart Association (NYHA) Class 3-4 symptoms, increased age or severe tricuspid regurgitation. Initial management consists of optimizing hormonal control of the underlying NET as well as medical therapies such as diuretics. In severe, symptomatic or progressive cases, surgical valve replacement may be considered, although the risks with these procedures remain high with a 30 day mortality of 18% in one series. Whilst bioprosthetic valves can fail from valve thrombosis, case reports have also highlighted the potential for recurrent plaque deposition and dysfunction in the implanted valve.

Somatostatin analogues (SSAs) have been used for symptomatic control in NETs, and more recently for their anti-proliferative properties. They act on the somatostatin receptors (SSTR), especially SSTR2 and SSTR5, mimicking the role of somatostatin in negative inhibition of hormonal production loops. Whilst different agents may have slightly different binding affinities to particular SSTRs, the two used in routine clinical practice – octreotide and lanreotide – have demonstrated efficacy in relieving the symptoms of carcinoid syndrome with randomized controlled trials showing a significant decrease in flushing, diarrhoea mirrored by a fall in biomarkers such as u5HIAA, which is a metabolite of serotonin.

Given that SSAs decrease the levels of circulating vasoactive substances, it has been hypothesised that SSA use has led to the decreasing incidence of CHD over time – from 55-70% in early series of patients with carcinoid syndrome to 10% in a recent screening study with 137 patients, 70% of whom had carcinoid syndrome. More broadly, better control of disease with both SSAs and targeted agents, with a reduction in tumour burden and hence the amount of vasoactive substances released, may slow the onset of CHD. In view of the above, we present a case series of 9 patients who developed clinically significant CHD despite very good symptom control on SSAs to underscore the clinical importance of regular echocardiographic monitoring in all patients with metastatic NETs.

Presentation

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Nine patients were identified from 4 centres (Royal North Shore Hospital, Peter MacCallum Cancer Centre, Queen Elizabeth Hospital, Auckland City Hospital) through consultation with colleagues, and retrospective chart review was undertaken to obtain the clinical characteristics of each case.

The characteristics of the nine patients are summarised in Table 1. The median age of the patients was 60; 3 were female. Overall, 6 cases arose from the small bowel, two from the large bowel and one from the pancreas. Six cases were classified as Grade 2 by WHO 2010 criteria, and three as Grade 1.

All the patients reported symptoms consistent with a secretory syndrome at diagnosis, with the most common symptom being diarrhoea (7 of 9 patients). All patients had elevated biomarkers of secretion at diagnosis (where tested) and received SSAs soon after diagnosis – being octreotide LAR in all but one case. Most patients (77%) received TTE at baseline; the remaining two patients did not receive echocardiograms at diagnosis (including the one pancreatic NET) but later presented with symptoms of CHD with echocardiography confirming the diagnosis. Of the patients who received baseline echocardiography, 2 patients did not have evidence of carcinoid heart disease. Seven of nine patients had well-controlled symptoms (such as pain, diarrhoea and flushing) after commencement of SSA. The other two patients had ongoing diarrhoea thought to be related to inadequate use of antidiarrhoeal agents despite repeated education, and one of these two had pain thought to be related to inadequate use of analgesia. There were no other functional symptoms for these two patients; their urinary 5-HIAA levels were elevated (Fig.1). Hormonal information regarding 24-hour uSHIAA and chromogranin A (CgA) (normalized to multiples of the upper limit of normal) are provided in accompanying figures (Fig.1, Fig.2).

More than half of the patients received peptide receptor radionuclide therapy (PRRT) in addition to SSA for treatment of their NET, and half received other systemic treatments (such as everolimus, sunitinib and chemotherapy).
The median time from NET diagnosis to CHD diagnosis was 23 months (range 4-52 months).

Moderate or severe tricuspid regurgitation was found in all patients, 5/9 had moderate pulmonary regurgitation or worse, and 1/9 had evidence of pulmonary hypertension. Most patients were NYHA class II/III on diagnosis of CHD but two acutely presented with class IV symptoms. One of the two patients had mild mitral regurgitation on baseline TTE and presented with severe symptoms 14 months after these results; the other had normal baseline TTE and presented 35 months after diagnosis with CHD. An illustrative picture of patient 3’s echocardiogram images is shown in Figure 3.

Eight of the nine patients required diuretics as part of their treatment, with the other patient not requiring any medical therapies. Five eventually received valve replacement for symptomatic CHD (tricuspid valve in all 5, and also the pulmonary valve in 2). None of these patients died within 30 days of surgery or had documented post-operative complications. Of the other four, one had stable symptoms on medical management alone, whereas three were deemed unsuitable due to rapid clinical deterioration (N=2) and poor performance status (N=1), ultimately succumbing to a combination of CHD and disease progression. A summary of the clinical course of the above patients is found in Figure 4.

Discussion

Somatostatin analogues have become a mainstay of NET management, and increasingly so with the publication of the PROMID and CLARINET trials\textsuperscript{18,19}. These two phase III placebo-controlled trials demonstrated improved time to progression and progression-free survival respectively in patients with well-differentiated NETs, and have established SSAs as a cornerstone of anti-neoplastic NET therapy. SSAs have been used in both functional and non-functional tumours with consequent improvements in outcomes. However, the good disease control afforded by SSAs in many cases should not lead to reduced vigilance in screening for CHD.
Our series demonstrates that patients with symptoms at presentation may still develop CHD on SSA therapy. We note that in all patients with available hormones, both CgA and 24-hour u5HIAA were elevated, pointing to the ongoing secretion of serotonin despite the relief of symptoms with SSAs and radiological stabilization of disease. This doubtless contributed to the progression of CHD in the reported cohort. CHD can develop months to many years after commencement of SSAs – with the median duration of SSA treatment prior to CHD diagnosis being 23 months in this cohort.

The persistent elevation of hormones despite the use of SSAs is a common problem in clinical practice. There are several reasons for the inadequate effect of SSAs. Tachyphylaxis, mediated by the downregulation of somatostatin receptors, limits the long-term efficacy of SSAs. Dose escalation of SSAs, whilst effective in some patients, is limited by concerns of possible QTc prolongation.

However, this side effect was only observed in SSA treatment of patients with acromegaly rather than NETs, and recent literature has shown that even this concern may be unfounded\(^\text{24}\). Telotristat is a novel agent which aims to reduce serotonin synthesis by inhibiting tryptophan hydroxylase 1 (TPH1), the rate-limiting enzyme in the process. A recent phase III trial demonstrated that telotristat could reduce both the frequency of bowel motions and urinary 5-HIAA levels in patients with carcinoid syndrome-related diarrhoea\(^\text{25}\). Although it is not licensed for this indication, telotristat may have future utility in treatment of patients with NET hormone production refractory to SSAs.

We note that one of the patients included in this series had a pancreatic primary. Despite regular CT imaging, no small bowel primary was identified. A recent series has shown that approximately 9% of pancreatic NETs secrete serotonin, with 1% overall manifesting as carcinoid syndrome\(^\text{26}\). We also note that two of the patients had diagnosis of CHD within a short period of diagnosis (4 months and 8 months), both with normal baseline TTEs. Although these periods are quite short compared to the usual period reported for CHD development, we note that both had markedly elevated 24-hour u5HIAA levels at diagnosis (at 7 and 11 times the upper limit of normal respectively), perhaps explaining the rapid pace of CHD onset. A urinary 5-HIAA level above 300μmol/24 hours was noted.

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in a study of 252 patients to predict for progression of CHD.\textsuperscript{27} We recognize that not all patients in the current series had regular hormonal assays; this real-life series emphasises the importance of regular hormonal monitoring in patients with diagnosed carcinoid syndrome even in the setting of symptomatic improvement.

The standard of care for CHD is surgical replacement of significantly affected valves. However, some patients may be sufficiently deconditioned or unstable that surgery poses an unacceptable risk. Of the three patients in our series who were deemed unsuitable for valve surgery, two had NYHA class IV symptoms, and the third had poor performance status. A recent study identified increasing age and NYHA class as predictors of poor prognosis.\textsuperscript{28} Early detection of CHD may prevent patients from having a worse NYHA class at diagnosis and reduce the risk of surgery. This may in turn allow patients to benefit from administration of further lines of systemic treatment without the risk of cardiac decompensation. Awareness, detection and appropriate management of intra- and peri-operative carcinoid crises may also decrease the risk of valve replacement.

The current series also raises intriguing questions regarding the value of regular screening for CHD in NET patients with a secretory syndrome but no clinical signs of CHD. Although recommendations exist for screening echocardiography at diagnosis as well as regular echocardiographic monitoring for those diagnosed with CHD, little evidence exists to guide screening in the patient without significant baseline valvular disease. The European Neuroendocrine Tumour Society (ENETS) recommend annual TTE monitoring in patients with established CHD\textsuperscript{11}, but does not specifically recommend a frequency of screening for asymptomatic patients, and American guidelines\textsuperscript{29} do not provide guidance as to the frequency of screening echocardiography. The United Kingdom and Ireland Neuroendocrine Tumour Society (UKINETS) states that all patients with midgut NETs or the carcinoid syndrome should be screened, and that screening may include NT-proBNP and TTE\textsuperscript{30}. The expert consensus by Davar et al recommended 6 monthly clinical assessment and measurement of NT-proBNP in patients with serotonin-producing NETs, with TTE recommended in those with a raised
NT-proBNP or clinical features suggestive of CHD. Considerable heterogeneity exists across centres with regard screening for CHD. This series has identified that patients without symptoms of CHD but with NET symptoms can develop CHD, and that earlier detection may be achieved by a surveillance programme (perhaps with yearly transthoracic echocardiograms). As more patients are being diagnosed with metastatic NET, earlier detection of CHD may result in large improvements in patients’ quality of life.

More specific, accurate and practical biomarkers are desperately needed for monitoring NETs, and future developments in this area may aid in screening for CHD. We note that elevated levels of serum proBNP, Chromogranin A, urinary 5-HIAA, or novel biomarkers such as Activin A may correlate to echocardiographic findings. Therefore, patients with persistently elevated proBNP (or other markers particularly urinary 5-HIAA) merit regular echocardiographic surveillance. Despite increasing interest and evidence for serum markers such as proBNP in the screening context, these have not been confirmed in large prospective studies and remain investigational at present. We feel that serum assays alone are not a substitute for TTE monitoring at this stage given the relative paucity of data supporting these investigations and the need for TTE to quantify the level of valvular dysfunction even if these markers were positive. Whilst cardiac magnetic resonance imaging (MRI) has been investigated in small populations and suggested in imaging CHD, its only established role in regurgitation to date is in determining the severity of regurgitation in cases where severity is indeterminate on echocardiogram.

In conclusion, carcinoid heart disease can occur even in patients whose “carcinoid” symptoms are well controlled on SSAs. Previously asymptomatic patients can present with advanced valvular disease which is not amenable to surgical intervention with consequently poor outcomes. All patients with metastatic NET and elevated hormonal assays should be regularly screened with transthoracic echocardiogram to facilitate early detection and timely intervention. This broader screening approach will require prospective trials for validation.
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Data availability statement: The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References


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Figure 1: Trends of 24-hour urinary 5-hydroxyindolacetic acid (u5HIAA) over time in study cohort

Figure 2: Trends of Chromogranin A (CgA) over time in study cohort. A semi-logarithmic graph has been used to better represent the wide variation in CgA levels between patients. Earlier values of Chromogranin A for patient 4 were unavailable.
Figure 3: Serial transthoracic echocardiogram images for patient 3. This patient had severe tricuspid regurgitation, mild aortic regurgitation and trivial mitral regurgitation diagnosed on follow-up TTE 8 months after baseline TTE. 3A: Four-chamber view at baseline. 3B: Colour-flow Doppler of tricuspid valve at baseline. 3C: Four-chamber view at CHD diagnosis: 3D: Colour-flow Doppler of tricuspid valve at CHD diagnosis.
Figure 4: Swimmers plot for included patients.
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<th>Other treatment prior to CHD</th>
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Table 1: Clinical characteristics of case series

Title: Vigilance for carcinoid heart disease is still required in the era of somatostatin analogues: Lessons from a case series

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