Carcinoid heart disease: two clinical cases and a review

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Abstract

We present two cases of metastatic carcinoid tumours, complicated by carcinoid syndrome and by cardiac valve involvement, a well-known, but infrequent, complication. Carcinoid tumours are generally more indolent than other cancers and may have a long asymptomatic phase. The symptoms of carcinoid syndrome generally manifest only once metastases to the liver have occurred. Cardiac involvement occurs in up to 50% of patients, and heralds a poor prognosis. However, a multidisciplinary team approach has improved the prognosis and quality of life for patients with carcinoid heart disease. Therapy includes somatostatin analogues and treatment for heart failure, removal of primary or metastatic tumour deposits, valve replacement in the presence of valvular involvement, and radioisotopes therapy.

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Introduction

Carcinoid tumours were first described more than 100 years ago by Lubarsh.[1] The term "carcinoid" means "carcinoma like", and was used to describe tumours that had a more indolent behaviour than that which was typical of carcinomas. As carcinoid tumours arise from neuroendocrine (enterochromaffin) cells, they can occur in a wide variety of organs, including the gastrointestinal tract, lungs, and ovaries. These rare tumours may go undiagnosed for many years, and patients may complain only of vague non-specific symptoms. We present two patients, each with a metastatic carcinoid tumour, and whose clinical presentations were complicated by cardiac involvement.

Case 1

A 57-year-old man presented with a three-year history of intermittent watery diarrhoea and frequent episodes of nausea and vomiting, unrelated to meals. Repeated gastric endoscopies at a secondary care hospital gave a normal result. He also complained of a 15 kg weight loss, unprovoked episodes of flushing, intense generalised pruritus, and ultimately fixed violaceous skin changes on his nose and cheeks. He was referred to Groote Schuur Hospital with right-sided heart failure and dyspnoea on minimal exertion (class III, New York Heart Association). On review, he was wasted, exhibited the rash as described, as well as telangiectasia of the face, and had right heart failure secondary to severe tricuspid regurgitation and a markedly enlarged liver, spanning 22 cm with a macronodular surface, suggestive of multiple hepatic metastases.

The urinary 5-hydroxyindoleacetic acid level (5-HIAA) at presentation was 820.8 µmol/24 hours (normal = 10.4-41 µmol/24 hours), whereas liver function tests and clotting

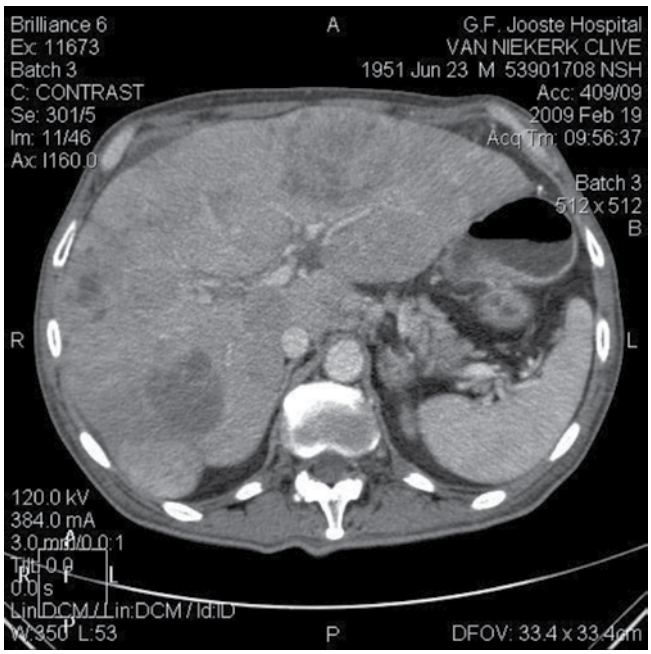

Figure 1: Contrast computed tomography of the abdomen at the level of T11 shows the markedly enlarged liver, with coexisting hypoechoic nodules, pathognomonic of metastatic disease

profiles were within normal ranges. Computed tomography (CT) of the abdomen confirmed extensive liver metastases of varying size (Figure 1).

An echocardiogram showed thickened and retracted tricuspid valve leaflets, resulting in severe tricuspid regurgitation and a dilated right ventricle and atrium. However, the left ventricle, left atrial dimensions and mitral and aortic valves were within normal limits. Due to the high cost of a diagnostic radiolabelled octreotide scan, and lack of an octreotide therapeutic option, an Iodine 123 MIBG (*m*-iodobenzylguanidine) scan was obtained. The I^{123} MIBG scan demonstrated multiple sites of abnormal uptake in the chest, liver and abdomen (Figure 2).

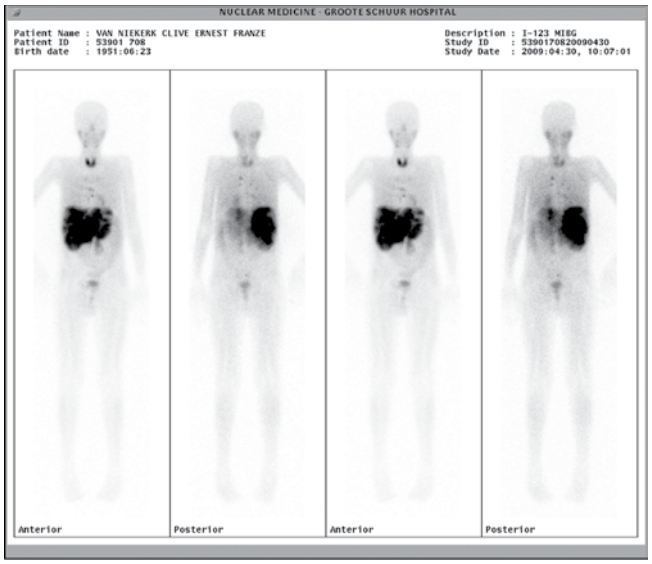

Figure 2: Whole body I^{123} MIBG scan demonstrates multiple sites of abnormal uptake in the chest, liver and abdomen, indicative of extensive metastatic disease

His cardiac failure improved with medical therapy, and 11.1GBq (300 mCi) I^{131} MIBG was administered. The patient died two weeks later. Inferior vena caval obstruction, thought to be due to tumour compression, was suggested as the cause of death at autopsy.

Case 2

In 2005, a 39-year-old woman with a confirmed amoebic liver abscess was managed at Groote Schuur Hospital with drainage and metronidazole. Over the next two years she developed intermittent watery diarrhoea and episodic facial flushing. Two years later, a routine follow-up CT scan demonstrated a new hypodense lesion within the liver. Histology of a plugged liver biopsy was highly suggestive of a metastatic carcinoid tumour. This was corroborated by markedly elevated urinary 5-HIAA (899 µmol/24 hours) and chromogranin A levels [> 585 U/l (normal = 0-23 U/l)].

Due to cost constraints, somatostatin receptor agonists were not available in our institution. Two years later, she developed symptoms of right-sided heart failure with features of pulmonary hypertension, together with daily watery diarrhoea and a minimum of two to three episodes per day of facial and truncal flushing, with each episode lasting between 30 minutes to three hours. On examination, she showed features of severe pulmonary hypertension and right heart failure, attributed to tricuspid regurgitation and mixed pulmonary valve disease. Her liver was massively enlarged, and exhibited a macronodular surface, suggestive of advanced metastatic carcinoid.

Urinary 5-HIAA levels increased to 1 975 µmol/24 hours in keeping with increased tumour burden. Repeat CT abdomen (Figure 3) suggested an isolated small bowel lesion with extensive hepatic metastases.

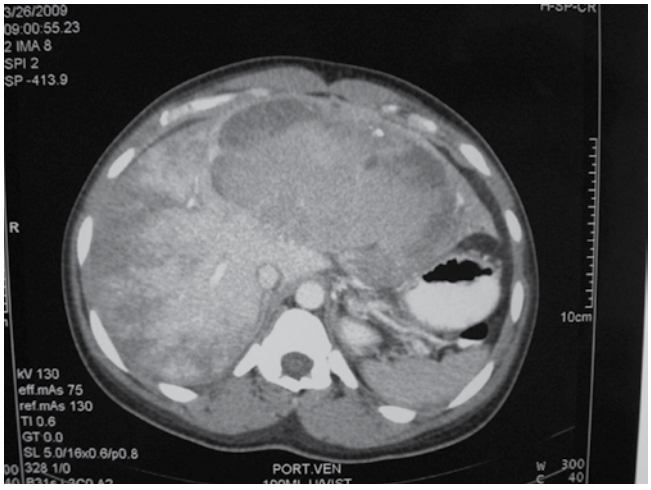

Figure 3: Double contrast CT scan at level of T10 showing grossly enlarged liver with a large hypoechoic lesion in the left lobe, and multiple smaller lesions in the right lobe, in keeping with metastatic disease

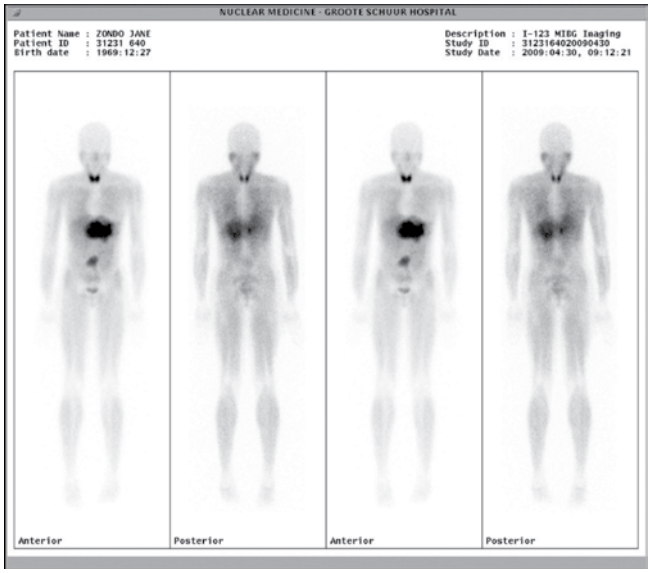

Figure 4: Whole body I^{123} MIBG scan showing abnormal uptake in the liver, as well as a focus in the mid-abdominal region

An I^{123} MIBG scan (Figure 4) demonstrated abnormal uptake in the mid-abdomen and liver, corresponding to the lesions seen on the abdominal CT scan. Echocardiography revealed markedly thickened and abnormal tricuspid leaflets with dilated right atrium and ventricle, coexisting with severe tricuspid regurgitation. The pulmonary valve appeared thickened and poorly mobile, resulting in severe mixed pulmonary valve disease, predominantly stenosis, with a transvalvular gradient of 40 mmHg.

Following initial optimisation of her cardiac failure with appropriate diuretics, she received a therapeutic dose of I^{131} MIBG 11.1 GBq (300 mCi). Thereafter, twice daily, subcutaneous octreotide (100 µg) for the management of the carcinoid syndrome was instituted. Her symptoms improved dramatically over the next year. The diarrhoea abated completely and flushing episodes were reduced to once a fortnight. Over the ensuing year, regular echocardiographs showed minimal progression of her valvular pathology.

Discussion

Epidemiology

The true incidence of carcinoid tumours is probably underestimated. The annual incidence of carcinoid tumours, diagnosed ante mortem, is about one to two per 100 000, according to the USA National Cancer Registry.[2,3] In comparison, the average annual incidence of carcinoid tumours in a large Swedish study, examining both post mortem and surgical specimens over 12 years, was 8.4 per 100 000.[3] Carcinoid tumours appear to have a bimodal age distribution, with a peak between 15-25 years, and another between 65-75 years of age. These tumours are most commonly found in the gastrointestinal tract (73.7%), in particular the small bowel (28.5%), appendix (18.9%) and rectum (11.4%), and the respiratory tract (25.1%).[3] Rare sites include the hepatobiliary and genitourinary tracts, most commonly, the uterus and ovary.[4]

Pathophysiology of carcinoid symptoms

The carcinoid syndrome, a constellation of symptoms associated with these tumours, develops in between 10-50% of patients with carcinoid tumours.[4-7] Patients with small bowel carcinoid tumours account for 75% of patients with the carcinoid syndrome.[8] Carcinoid tumours produce various secretory products such as serotonin, histamine, tachykinins, kallikrein and prostaglandins. Histamine and kallikrein are likely mediators of pruritus and flushing, whereas serotonin is the most likely to induce diarrhoea.[9] In the setting of liver metastases, or direct secretion of these substances into the systemic circulation (bypassing the portal system), these substances produce systemic effects,

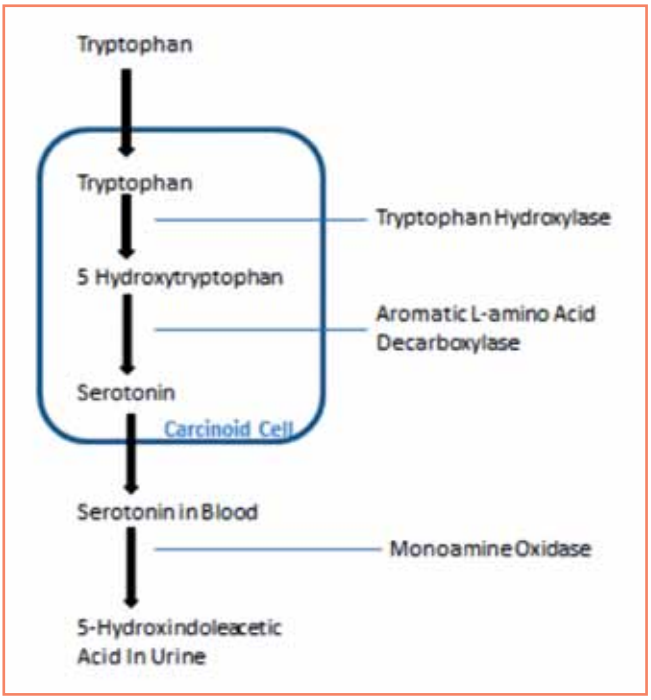

Figure 5: Metabolism of serotonin

leading to the characteristic symptoms.[10] The differences in the clinical and biochemical features relate largely to altered and aberrant metabolism of tryptophan. Foregut tumours (arising from stomach, duodenum, and bronchi) and ovaries frequently lack the enzyme aromatic L-amino acid decarboxylase (see Figure 5). Consequently, they are unable to produce serotonin and few symptoms occur. Hindgut tumours (from transverse, descending colon and rectum) generally lack the enzyme tryptophan hydroxylase, and are therefore not associated with carcinoid symptoms. By contrast, midgut tumours (originating from the jejunum, ileum, appendix and ascending colon) generally have all the necessary enzymes to convert tryptophan to serotonin, and are most likely to produce the classical carcinoid syndrome.

Diagnosis

The diagnosis is reliant on either positive histology, or elevated 24-hour urinary 5-HIAA levels. The latter test has a sensitivity of 75% and a specificity of up to 100%, provided that the use of certain drugs and foods are excluded.[11] Chromogranin A, by contrast, is a non-specific marker, and is often raised in patients with a carcinoid tumour. Depending on the cut-off values and assays used, its sensitivity and specificity are 75% and 84%, respectively.[12]

Carcinoid heart disease

Patients with carcinoid syndrome have a propensity to develop plaque-like deposits consisting of smooth muscle, myofibroblasts, connective tissue and an overlying epithelial layer on heart valves, in particular the undersurface and

chordae tendineae, and endocardium. Retraction and fixation of valves ensues, leading to severe deformity and resultant regurgitant and stenotic lesions.[10,13]

Pathogenesis

The right heart chambers and tricuspid and pulmonary valves, which receive blood directly from the liver, are the most commonly affected sites. However, right-sided lesions may also occur when the veins draining primary or secondary lesions bypass the portal circulation, as is the case with ovarian carcinoids. Left-sided cardiac involvement is far less common (less than 10%), as the lung parenchyma inactivates many of the secreted products. Left-sided lesions may occur with primary lung carcinoids, or in the presence of cardiac defects such as atrial and ventricular septal defects. Actual metastases to the myocardium account for fewer than five per cent of cardiac lesions associated with carcinoids.[14]

While it is still debated as to whether serotonin, or another co-secreted hormone or by-product, is causative in the pathogenesis of fibrosis, evidence is mounting in favour of serotonin itself as the causative agent.[14-18]

The vast majority of serotonin (90%) originates from the gastrointestinal tract, predominantly from the intestinal enterochromaffin cells (95%), while only 10% is produced in the brain.[17] Indirect evidence of the role of serotonin in the pathogenesis of valvular damage is that patients with cardiac involvement tend to have higher levels of urinary 5-HIAA than those without cardiac involvement.[10,15,19,20] Drugs known to inhibit the metabolism of serotonin, e.g. fenfluramine and dexfenfluramine, predispose to identical valvular heart lesions. Additionally, a meta-analysis of Parkinson's disease treatment found that 22% (53/245) of patients treated with pergolide and 34% (35/102) of patients treated with cabergoline, both agonists of serotonin 2B (5HT2B) receptors, had moderate-to-severe valve involvement, not unlike that seen in carcinoid heart disease.[21] While the exact mechanism is still unclear, Roth suggests that serotonin activates the G-protein-coupled 5HT2B receptor, leading to increased production of protein kinase B via activated phospholipase C. This leads to eventual stimulation of mitogenic pathways through activation of transforming growth factor beta (TGF-β), which may be responsible for the fibrous changes on heart valves. In a small study of 30 patients, over 80% of tumours produced TGF-β.[18] Additionally, rats injected with high doses of daily serotonin for three months, developed increased cardiac mass, cardiac fibrosis and valvulopathy.[22] Concomitant use of a serotonin receptor antagonist inhibited these changes.[23] Whether treatment with serotonin antagonists can prevent cardiac progression in humans is not known.

Other potential mediators of carcinoid-related fibrosis may involve kinins, such as tachykinins, which are known to stimulate DNA synthesis in fibroblasts. Neurokinin A and substance P have also been linked to cardiac fibrosis.[17]

Clinical features and diagnosis of carcinoid heart disease

The lag phase between the onset of carcinoid symptoms and development of cardiac involvement is usually around two years. Often, the heralding symptoms are easy fatiguability and reduced performance status. Clinical features are right ventricular enlargement and cardiac valve lesions, specifically tricuspid regurgitation and pulmonary stenosis and/or regurgitation. With disease progression, patients develop the signs and symptoms of right heart failure.[24]

Echocardiography is the imaging modality of choice in assessing the presence and degree of cardiac involvement. Typically, the valve leaflets appear thickened and have reduced mobility. Often the valve annulus is reduced, leading to stenotic lesions. The chordae tendineae become thickened and retracted, restricting mobility of the attached valve leaflets with resultant valve regurgitation.[24]

Natural history

Patients with carcinoid tumours progress slowly and develop symptoms often only 10-12 years after development of the primary lesion.[25] Five-year survival rates from diagnosis depend on the site of origin, size at diagnosis, presence or absence of metastases, and whether the carcinoid syndrome coexists. Overall, survival rates range from 50-80% for small bowel tumours without cardiac involvement.[3,26,27] The presence of cardiac involvement indicates a particularly poor prognosis, with survival rates diminishing to approximately 30% at five years.[10,16] Symptoms of cardiac failure, particularly right heart failure, eventually develop in up to 50% of patients with carcinoid syndrome, whereas heart failure is present in up to 20% of patients at the time carcinoid syndrome is diagnosed.[14,15]

Therapy

Medical therapy

Management of carcinoid tumours needs to be individualised, and includes medical, surgical and radioisotope therapy. The European Neuroendocrine Tumour Society[27] published treatment guidelines for gastrointestinal neuroendocrine tumours in 2008. With respect to survival, therapies aimed at reducing tumour bulk and restoring normal cardiac anatomy have been shown to be most efficacious. However, both medical management, as well as radioisotope therapy, play an important role. Medical management includes treatment and control of heart failure using standard medications,

and symptomatic relief of carcinoid symptoms with the use of somatostatin analogues (octreotide). Slow-release formulations, albeit expensive, are available, offering convenient single daily dosing regimens. Symptomatic relief is achieved in 70% of patients on somatostatin analogue therapy.[18] Although medical management significantly improves carcinoid symptoms, on its own, it does not alter survival. Although modest reductions in 5-HIAA levels can be achieved with octreotide therapy, regression of cardiac lesions and improved mortality has not been shown in studies.[28]

Radioisotope therapy

Increasingly, palliation with tumour-targeted therapy, using Ytrium 90 or Lutetium 177m labelled Octreotide, as well as I^{131} MIBG, is being used to offer patients significant improvement in carcinoid symptoms. Diagnostic scans with Indium 111 Octreotide detect neuroendocrine tumours with a sensitivity of 67-100%. I^{123} MIBG, traditionally used for detecting metastatic adrenal medullary tumours, has also found application in treating patients with the carcinoid syndrome. Up to 70% of carcinoid tumours avidly take up MIBG, making I^{131} MIBG an attractive tumour-specific treatment option. SSafford et al[29] published a 15-year retrospective review of 98 patients treated with I^{131} MIBG as palliative carcinoid treatment. Overall, the symptoms of 49% of patients with metastatic disease improved. Interestingly, patients who experienced symptomatic improvement lived longer (5.76 years) compared to those whose symptoms were unchanged (2.09 years). A > 50% reduction in their urinary 5-HIAA levels was achieved in 37% of patients, and 76% had minimal radiological evidence for reduction of tumour burden.

Radiolabelled octreotide and MIBG target different receptors. As such, combination therapy may have a synergistic action.[30]

Surgery

The mainstay of treatment is surgery, which is aimed at reducing tumour bulk and improving carcinoid symptoms. With or without cardiac involvement, reduction in total tumour burden has been shown to improve survival.[31,32] These include procedures such as selective arterial tumour embolisation, chemoembolisation, laser-induced thermotherapy, radiofrequency ablation and surgical debulking of both primary and metastatic lesions, all of which have shown benefit.[33] Five-year survival rates in patients who have surgically resectable disease (including liver metastases) are > 60% compared to 30% in patients with irresectable disease. The vast majority (over 90%) of patients experience symptomatic relief following surgical debulking.[31,34] Current recommendations advise hepatic resection in patients where the primary tumour, locally advanced disease and > 90% of the hepatic tumour burden is deemed resectable.

Cardiac surgery, specifically valve replacement, has conferred a significant survival benefit to patients with cardiac involvement. Since its introduction, the perioperative mortality has declined from 35% to nine per cent in the Mayo Clinic series.[35] The reduction in perioperative mortality appeared to improve when cardiac surgery was offered to patients with a better baseline performance status. Quality-of-life and survival has improved from a mean of 11 months to up to four years.[35] Current surgical indications in those with cardiac valve disease include impaired exercise tolerance, progressive fatigue, and worsening ventricular function in the presence of controlled metastatic carcinoid disease.

Valve replacement is preferred to valve repair, due to the irreversible retraction and fixation of the valve apparatus. The choice of prosthesis needs to be individualised. The inherently shortened longevity of bioprosthetic valves, compared with metal valves, and the incumbent need for anticoagulation should be considered carefully, since metastatic tumour deposits are at high risk of haemorrhage.[24]

Conclusion

Carcinoid tumours are rare malignant tumours of neuroendocrine origin. In addition to the typical syndrome, these tumours have a propensity to involve the heart in about 50% of patients with carcinoid syndrome. The use of effective serotonin antagonists has led to improvement in quality of life, while a proportion of patients with both the carcinoid syndrome and cardiac involvement have had survival benefit from a combination of medical therapy, radioisotope therapy and surgery.

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