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Review

The clinical presentation and management of carcinoid heart disease

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ABSTRACT

Carcinoid heart disease is a major cause of morbidity and mortality in patients with metastatic neuroendocrine tumours (NETs). Although cases of carcinoid syndrome and severe carcinoid heart disease requiring urgent intervention are well described, many patients with significant carcinoid heart disease may have insidious symptoms or even be asymptomatic. As haemodynamically significant carcinoid heart disease may be clinically silent, specific and individualised considerations must be made as to the most appropriate clinical criteria and time point at which surgical valve replacement should be undertaken in patients with carcinoid heart disease.

1. Introduction

Carcinoid heart disease (Hedinger syndrome) is a major cause of morbidity and mortality in patients with metastatic neuroendocrine tumours (NETs). These tumours are rare, occurring in 1.2–2.1 per 100,000 people [1], but approximately 50% of patients will develop carcinoid syndrome, of which 20–50% will develop carcinoid heart disease [2,3]. Carcinoid heart disease is mediated by vaso-active substances secreted by the tumours, including 5 hydroxytryptamine, (5-HT, serotonin), prostaglandins, histamine and tachykinins which lead to deposition of endocardial plaques composed of fibrous tissue [4]. The deposits occur primarily on the downstream side of the valve leaflets; i.e. on the ventricular aspect of the tricuspid valve and the pulmonary arterial side of the pulmonary valve [5]. The disease is characterised by retraction and fixation of predominantly the right-sided valve leaflets, leading to a combination of valvular regurgitation and stenosis (Fig. 1), which ultimately can progress to right heart failure [6]. The left side of the heart is relatively protected as the lungs filter the vaso-active peptides, inactivating them in the pulmonary circulation before they reach the left atrium. Therefore left sided disease is seen only in patients with bronchial carcinoid or patent foramen ovale or in those with poorly controlled, severe carcinoid syndrome that overwhelms the pulmonary degradative capacity [7].

Valve surgery is the only definitive treatment option for patients with carcinoid heart disease, with contemporary studies now demonstrating significantly improved survival associated with valve replacement compared with studies in previous decades [8,9]. There is no clear consensus surrounding the indications for, and optimum timing of, surgical intervention in patients with carcinoid heart disease.

2. Pathophysiology of carcinoid heart disease

The precise pathways responsible for the development of carcinoid heart disease are still uncertain and the disease is likely to be multifactorial. However, there is a strong body of evidence that serotonin is involved in the pathogenic process. Firstly, serotonergic drugs used in the treatment of obesity, migraine and Parkinsons's disease have been demonstrated to cause valvular fibrosis [10]. Secondly, long-term serotonin administration has been shown to induce valvular fibrosis in rats [11]. Thirdly, urinary 5-hydroxyindoleacetic acid (5-HIAA), which is indicative of the amount of serotonin production, is significantly higher in patients with carcinoid heart disease compared to those without cardiac involvement [4,12]. However more than 50% of patients with elevated circulating serotonin levels do not develop carcinoid heart disease [9] and other biochemical mediators, such as activin A [13] and connective tissue growth factor [14] have also been associated with the development of the disease.

Distinct from carcinoid heart disease, the myocardium can also be affected by direct infiltration of the neuroendocrine tumour. Myocardial metastases occur in around 4% of patients with metastatic NETs [3]

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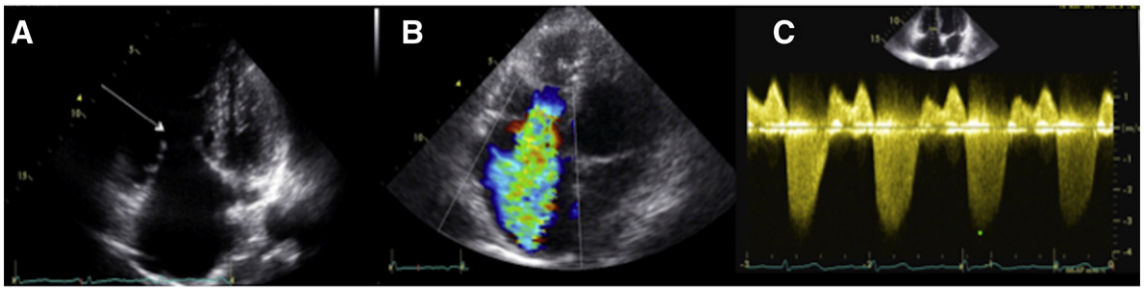

Fig. 1. Echocardiographic features of carcinoid heart disease: A. Dilated right heart, with thickened, retracted tricuspid valve leaflets. B. Colour flow Doppler revealing severe jet of tricuspid regurgitation filling a dilated right atrium. C. Continuous wave Doppler showing dense jet of tricuspid regurgitation.

but this may be an underestimation due to the limited resolution of traditional imaging modalities [15].

3. Multi-modality imaging of carcinoid heart disease

Echocardiography is the principal imaging modality used in the assessment of carcinoid heart disease, but other modalities are important, particularly in the quantification of the severity of disease. Cardiac magnetic resonance imaging (MRI) overcomes the issue of sub-optimal visualisation of the right-sided heart valves and has the advantage of enabling accurate quantification of regurgitant volumes and right ventricular ejection fraction [16,17]. This information is pivotal to the decision-making process for the long-term management of the patient. Carcinoid plaques can also be directly visualised using delayed-enhancement imaging with gadolinium [18]. Positron emission tomography can also identify cardiac metastases using synthetic radiolabelled octreotide with radio-nuclide tracers such as ^{68}gallium [19] and ^{18}F-dihydroxy-phenyl-alanine [15].

4. Impact of carcinoid heart disease on symptoms and survival

Whilst the majority of patients with severe carcinoid heart disease will present with signs of right heart failure (dyspnoea and peripheral oedema) [1], it is important to note that a substantial proportion of patients with cardiac involvement have no signs or symptoms. Clinical assessment including New York Heart Association (NYHA) classification, and physical examination to identify cardiac murmurs or peripheral oedema are rarely sufficient, even with disease severe enough to warrant valve replacement [20]. There is no evidence that patients with NETs are predisposed to particular cardiac arrhythmias.

Neuroendocrine tumours are slow-growing, with well-differentiated tumours (grade 1, proliferative index Ki67 <2%) conferring a median survival of 124 months [21] versus a significantly reduced survival of around 48 months in patients with concomitant carcinoid heart disease [22]. Carcinoid heart disease in conjunction with NYHA class III or IV symptoms has a particularly poor prognosis with a median survival of 11 months [23]. Age and severe tricuspid regurgitation are independent risk factors for death in patients with cardiac involvement [24]. Right sided heart failure caused by carcinoid heart disease is the commonest cause of death in this patient group (around 50%) [25] with tumour progression responsible for around 45% of deaths. These survival data provide further justification for routine cardiac screening of all patients with metastatic NETs and may provide a rationale for earlier and/or more aggressive intervention to prevent symptoms of right heart failure. At our centre all patients with hepatic metastases and/or carcinoid syndrome have annual transthoracic echocardiography to screen for carcinoid heart disease.

With regard to the clinical course of cardiac involvement, high urinary 5HIAA levels are a predictor of progression of carcinoid heart disease [26]. This finding was corroborated by Bhattacharyya et al. [27] who demonstrated that a urinary 5HIAA level greater than 300 μmol/24 h and more than 3 flushing episodes per day are independent predictors of the development or progression of carcinoid heart disease.

5. Guidelines for management of carcinoid heart disease

Consensus European Neuroendocrine Tumor Society (ENETs) guidelines state that annual echocardiography is mandatory as part of the routine surveillance of patients with carcinoid heart disease [28]. However, current American and European guidelines do not address the issue of how to best manage patients with asymptomatic or minimally symptomatic carcinoid heart disease [29–32]. Advanced carcinoid heart disease is easy to identify on a transthoracic echocardiogram; however, in the early stages of the disease, the diagnosis can be challenging. Subtle thickening of the tricuspid valve leaflets and subvalvular apparatus, with mild tricuspid regurgitation may be a non-specific finding and it is for this reason that patients should be screened in a serial fashion, with comparisons made to previous echocardiograms. Echocardiography is the gold standard for the detection of carcinoid heart disease and should be performed by an echo-sonographer with personal experience of at least 200 examinations per year [33].

A variety of biomarkers have been identified for the presence and severity of carcinoid heart disease. The most useful to date is N-terminal pro-brain natriuretic peptide (NT-proBNP) which is recommended in the UK & Ireland Neuroendocrine Tumour Society (UKINETS) guidelines [34] as a screening tool for carcinoid heart disease (level of evidence 1b) in patients with midgut NETs, with or without hepatic metastases, and all patients with the carcinoid syndrome. Chromogranin A has also been shown to be a sensitive marker for cardiac involvement in patients with NETs [35]. As therapeutic options and therefore prognosis, for patients with NETs improve, an awareness of how to best identify and manage carcinoid heart disease, and the optimal time point to consider valve replacement become increasingly important.

6. Medical and surgical interventions for carcinoid heart disease

Carcinoid heart disease is a rare, complex disease, and should be managed in a specialist centre, with multi-disciplinary team input from oncologists, cardiologists, endocrinologists, gastroenterologists and surgeons (colorectal, hepatobiliary and cardiothoracic) [5]. A holistic approach is essential in the management of patients with carcinoid heart disease, reflecting the patient's preferred treatment option, the cardiac manifestations of the tumour, and the effect of any cardiac disease on the management of the underlying NET.

There is no current evidence to suggest that medical interventions such as somatostatin analogues, hepatic artery embolisation or systemic chemotherapy have a beneficial effect on the progression of valvular disease [26] and bacterial endocarditis prophylaxis is not indicated in patients with carcinoid heart disease [36]. General measures to treat right heart failure, such as the use of loop diuretics and fluid and salt restriction may improve symptoms of oedema. However these measures can be deleterious in advanced right ventricular failure due to depletion of intravascular volume further reducing cardiac output, leading to