Epicardial mass and Valvular heart disease: What is the relation?

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Abstract

A solitary apical epicardiac mass was detected in a 58-year-old male, presenting with exertional dyspnoea. Radiological follow-up showed stable size of this mass. However, one year later the patient developed symptoms suiting carcinoid syndrome. ^{68}Gallium DOTANOC Positron emission tomography-CT showed markedly increased somatostatin receptor expression at multiple sites, including the epicardiac mass. In addition, the patient developed symptomatic carcinoid heart disease, with severe right-sided valvular dysfunction leading to congestive heart failure, for which valvular surgery was performed.

We report this remarkable case of carcinoid disease that presents all the possible aspects of cardiac involvement, followed by a discussion concerning current treatment strategies in carcinoid heart disease.

Key words: *Carcinoid disease, Carcinoid syndrome, Carcinoid heart disease, Carcinoid heart metastasis*

1. Introduction

Carcinoid disease can lead to carcinoid syndrome, due to secretion of vasoactive tumour products. These vasoactive substances are metabolized in the liver and lungs. When extended liver metastasis is present, its inactivation capacity is exceeded, and carcinoid heart disease, typically involving the tricuspid and pulmonary valve, can develop. In metastasized carcinoid, metastasis to the heart is rare. When symptoms of heart failure develop, valvular impairment is often already severe and the question is raised if and when heart surgery should be performed.

We present a patient with a metastasized carcinoid disease with carcinoid syndrome, cardiac metastasis and severe carcinoid heart disease.

2. Case Report

A 58-year old male was referred for cardiac evaluation in our out-patient clinic because of increasing exertional dyspnoea during cycling. His medical history consisted of coronary angioplasty of the right coronary artery and recent implantation of a double chamber pacemaker because of symptomatic atrio-ventricular block. A physical examination demonstrated no signs of cardiac dysfunction. Transthoracic echocardiography (TTE) showed mildly decreased left ventricular ejection function, due to known inferior hypokinesia, and mild concentric left ventricular hypertrophy. Furthermore, mild mitral valve regurgitation secondary to annular dilatation, mild tricuspid valve regurgitation, with pacemaker lead in situ, and mild pulmonary hypertension were noted. The morphology and mobility of all heart valves were normal. Remarkably, an apical epicardiac mass was detected, measuring 21 by 31 mm (figure 1). Additionally, by performing ecg-gated computed tomography (CT) scan of the heart, this solitary cardiac tumour with apical and epicardial localisation was confirmed, without signs of local invasion

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or mass effect. Further work-up with stress echocardiography showed no signs of ischemia nor aggravation of mitral valve regurgitation. It was assumed that this epicardiac mass could not be held responsible for the exertional dyspnoea the patient presented with. Since taking a biopsy is cumbersome, a follow-up CT was recommended. This CT-scan at 6 months showed no change in the size of the mass, as well as no evidence of invasion or invasion into the myocardial wall.

One year after the detection of this cardiac mass, the patient was referred to an endocrinologist because of weight loss, hot flushes, intermittent diarrhoea and gooseflesh. Urinary dosage of 5-HIAA was highly elevated (454mg/24h, normal <8.0mg/24h). Additionally, an abdominal CT scan revealed the presence of diffuse hypervascular liver metastases, also suggestive for carcinoid disease. Liver biopsy confirmed the presence of neuro-endocrine tumor, grade 2. A positron emission tomography (PET)-CT using ^{68}Gallium DOTANOC (a PET radiotracer specifically binding to somatoreceptors) demonstrated intense somatostatin overexpression of the epicardiac apical mass (Figure 2), lesions in the liver, mesenterial lymph nodes, mesenterium and multiple sites in the skeleton. Diagnosis of metastasized carcinoid disease with carcinoid syndrome was withheld, most likely originating from a mass in mesenterial fat.

Long-acting release (LAR) somatostatin was started at a dose of 20mg every 28 days by intramuscular injections. Initially, flushing and diarrhoea episodes improved. However, repeated evaluation of 5-HIAA, NSE and ^{68}Ga-DOTANOC PET-CT scan showed progressive carcinoid disease. Because of this, somatostatin dose was increased and the patient was referred for radionuclide therapy (PRRT), consisting of high dose of 177Lu-Octreotate, somatostatin analogue. With time, the patient

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developed limiting exercise intolerance with dyspnoea, New York Heart Association (NYHA) functional classification grade 3. Cardiac re-evaluation demonstrated clinical signs of right heart failure with ascites and peripheral oedema. Echocardiography, two years following the last one, now revealed evolution to severe restrictive tricuspid valve disease with valvular and subvalvular thickening, malapposition of the leaflets, and consequently severe tricuspid regurgitation (figure 3). Furthermore, moderate pulmonic valve regurgitation, moderate right ventricular (RV) dilatation and dysfunction, and mildly decreased left ventricular (LV) function with D-shaping were present. Additionally, diagnosis of liver cirrhosis was withheld. Liver cirrhosis has been reported as a rare complication in patients presenting with liver metastasis treated with PRRT. However, it is likely that the combination of PRRT and the presence of right heart failure both are responsible for the development of liver cirrhosis in this patient. Diuretics were initiated (bumetanide 1mg once daily), somatostatin LAR dose was increased (60mg every 2 weeks) and interferon-alfa was added to the therapy. After a discussion in the heart-team, indication for surgery was postponed because of better control of heart failure symptoms (NYHA class grade 2) since administering diuretics, but also because of progressive carcinoid disease and the presence of liver cirrhosis (CHILD PUGH class: B). A second opinion was prompted in another heart-centre, where it was decided to perform tricuspid and pulmonary valve replacement with bioprostheses, mitral valve plasty, closure of left atrial appendage and placement of an epicardial LV lead (figure 4). Initially, the patient felt less dyspnoeic and diuretics could be stopped. Unfortunately, 4 months later, the patient developed intestinal obstruction due to abdominal tumour mass and fibrotic reaction, a known

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complication of carcinoid disease. Urgent laparotomic right hemicolectomy was performed, with complicated post-operative recovery. Thereafter, because of oncological progression, everolimus was added to somatostatin therapy. However, dyspnoea NYHA class grade 3 occurred again. Unfortunately, six years after the diagnosis of metastasized carcinoid disease and 15 months after the cardiac surgery, the patient died.

3. Discussion

A carcinoid tumour is a neuroendocrine malignancy, most often originating in the gastro-intestinal tract (64%), the bronchopulmonary system (28%), or less frequent from neuroendocrine cells elsewhere in the body. Typically, it is associated with production of serotonin (5HT), secreted as 5-hydroxyindolacetic acid (5HIAA) in urine, but many other vasoactive substances (histamine, tachykinins, prostaglandins) can also be secreted. The risk for metastases is proportional to tumour size and they are most often located in regional lymph nodes, liver, bone or lung. Metastasis to the heart is rare, the reported incidence is about 4% [1]. Tumour products can be inactivated in the liver, but when degradation capacity is exceeded, due to extended liver metastasis, carcinoid syndrome (CS) may appear. As in our case, cardinal features of CS consist of flushing and diarrhoea, but also asthma-like symptoms, abdominal pain and pellagra-like skin lesions can be present. In advanced carcinoid disease, tumour products reach the heart, and in 14 to 41% carcinoid heart disease (CaHD) can develop. Overstimulation of $5HT_{2B}$-receptors, located in the heart valves and endocardium, but also other vasoactive substances excreted by the malignant cells, lead to cardiac involvement [2-3]. Deposition of dense fibrotic plaques, predominantly in the right side of the heart, leads to leaflet thickening and shortening, annular constriction and fusion of the subvalvular apparatus. This

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can lead to severe regurgitation or stenosis, most often at the tricuspid and/or pulmonary valve, with the pathognomonic echocardiographic image of rigid and almost fixed position of the leaflets. Subsequent right-sided heart failure develops in 80% of patients with CaHD. Lesions at the left side of the heart are less frequent, because of serotonin metabolization in the lung. Left-sided heart involvement is more likely when a right-to-left shunt or a bronchial carcinoid tumour is present. In the early phase, CaHD can be asymptomatic or well tolerated (fatigue, exertional dyspnoea), but progression leads to worsening dyspnoea, anasarca and cardiac cachexia.

Serotonin receptor antagonists or somatostatin analogues are used for CS-symptom relieve. In non-metastatic carcinoid disease, surgery is the only potentially curative therapy. However, in metastatic disease, anti-tumoural treatment has limited response rate. Somatostatin analogues or interferon-alfa rarely decrease tumour size, but they do have a tumouristatic effect. Hepatic embolization can reduce tumour bulk and control symptoms. There is no current evidence that one of these interventions influences progression to CaHD [3-5].

Since treatment of carcinoid disease has improved, cardiac impairment has become an important factor that worsens quality of life, and even leads to excess mortality [5]. Symptomatic right heart failure treatment with diuretics, fluid and salt restriction can be considered, but the only definitive treatment for the valvular disease is surgery. First results after valvular surgery showed high perioperative mortality. This has significantly improved over the last decades (30-day mortality declining from 17% before 2000, 7.2% between 2000 and 2009, and 3.7% between 2010 and 2012), due to increasing surgical expertise, better patient selection and better perioperative management of possible carcinoid crisis

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or low-output failure [5]. Also, survival has increased notably, with survival rates at 1, 5 and 10 years of respectively 69%, 35% and 24%. Likewise, significant symptomatic improvement was noted after valvular surgery [5]. Observational reports have showed that advanced NYHA functional class, pre-operative need for diuretics, presence of ascites, pre-operative chemotherapy, age, tobacco use, left sided heart disease, RV size and RV dysfunction are parameters for worse postoperative outcome [5-8].

The used type of valvular prosthesis has changed over time. Initially, mechanically valves were used, but problems with anticoagulants along with coagulopathy due to liver disease led to morbidity. Bioprosthetic valves are now used. In cases where bioprosthesis valve dysfunction was noted, not carcinoid involvement with new fibrotic deposits, but thrombosis was more often the cause of dysfunction. Therefore, bioprostheses in tricuspid and pulmonary valve position with concomitant right ventricular outflow tract (RVOT) enlargement is now the recommended strategy [7-8]. In the pulmonary valve position, surgical valvulotomy, homografts, and stentless bioprosthesis are not recommended anymore [9]. When moderate or severe mitral valve regurgitation is present, or if a patent foramen ovale is present, concomitant repair should be performed.

The positive trend in outcome after valvular surgery in carcinoid heart is also a result of careful perioperative prevention of carcinoid crisis. Perioperative administration of intravenous somatostatin, and avoidance of drugs that precipitate vasoactive drugs (opioids, atracurium, dopamine, adrenaline, epinephrine) should be prompted [6]. Therefore, a careful and experienced anaesthesiological assessment is warranted.

Symptomatic patients with CaHD, but also asymptomatic patients with signs of progressive right heart disease

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(enlargement or dysfunction) or even asymptomatic patients with elevated right atrial pressure before undergoing hepatic surgery, can be considered for elective valvular heart surgery.

Indication for valvular surgery should be made timely, considering that severe symptomatic CaHD, but also advanced metastatic disease, both lead to worse postoperative outcome and survival. Consideration for heart surgery should be prompted with careful risk-stratification in a multidisciplinary and experienced team in this field.

4. Conclusion

We presented a case of a cardiac carcinoid metastasis in a patient with carcinoid disease and carcinoid syndrome, who also developed severe right heart failure due to carcinoid heart disease. As seen in our patient, fixated and rigid right ventricular valve leaflets are the hallmark of carcinoid heart disease due to fibrotic deposits leading to severe valve regurgitation or stenosis.

Despite extensive oncological treatment in metastasized carcinoid disease, progression to carcinoid heart disease with severe right-sided valvular dysfunction and subsequent congestive heart failure can occur. Subsequent heart failure has an important impact on quality of life, and leads to excess morbidity and mortality. Discussion about the indication and timing of valvular surgery was raised. The presence of pre-operative advanced stage of heart failure and advanced oncological disease have shown a worse post-operative outcome. In the last decades, perioperative mortality has much improved, due to better patient selection, surgical techniques and experience, handled in a multi-disciplinary and experienced team. However, evidence concerning timing of surgery in carcinoid heart disease, is based only on observational studies.

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Figures

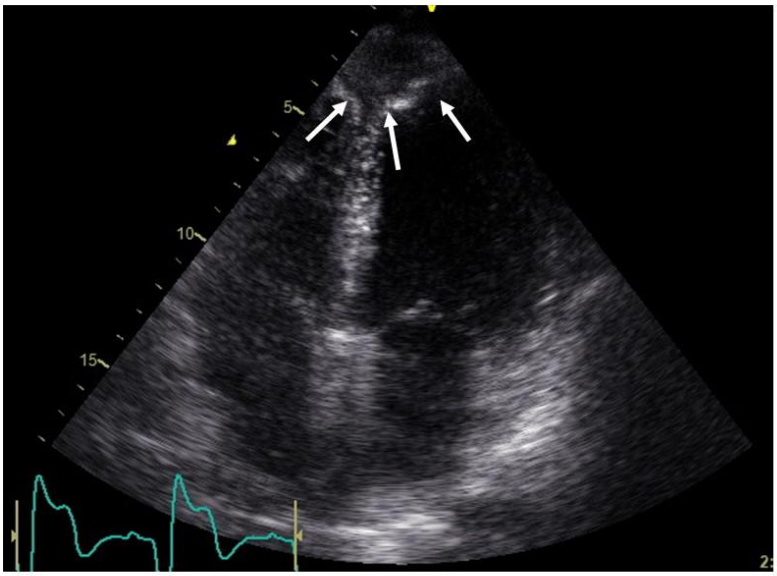

Figure 1. Transthoracic echocardiography (Apical 4 chamber view), showing apical epicardiac mass, 21 by 33mm, a carcinoid metastatic lesion (White arrows).

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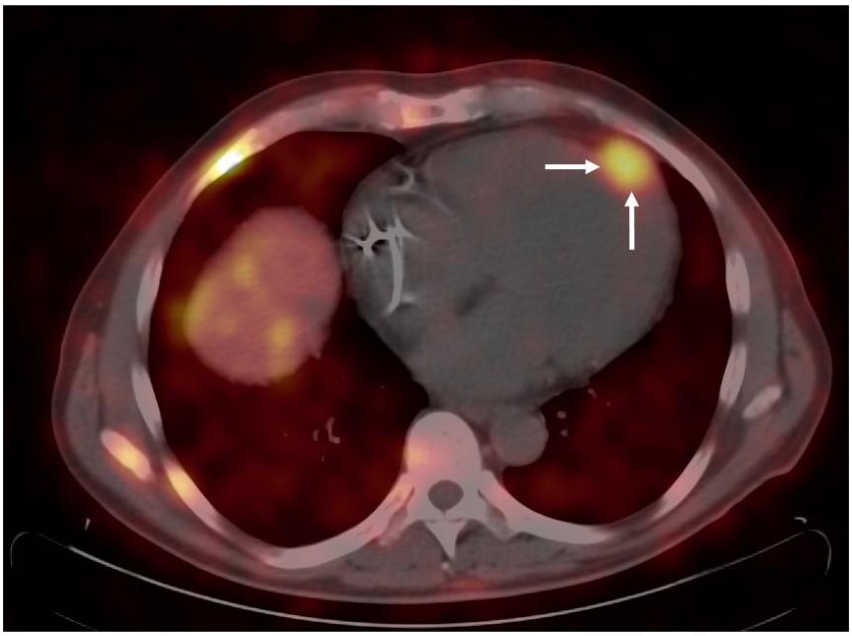

Figure 2. ^{68}Ga-DOTANOC PET-CT scan showing intense somatostatin overexpression of the epicardiac apical mass (White arrows).

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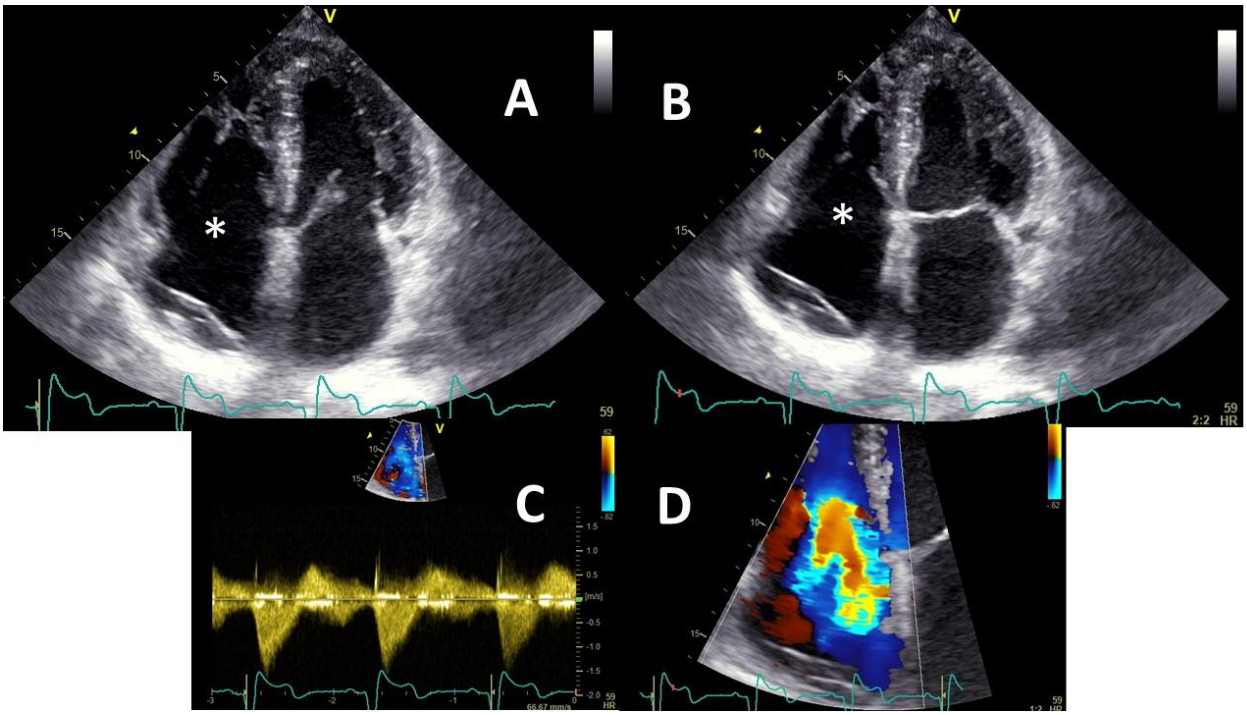

Figure 3. Transthoracic echocardiography (Apical 4 chamber view) showing (A) opened tricuspid (*) and mitral valve during diastole, while in systole (B) mitral valve closes normally but a fixed semi-open position of the tricuspid valve (*) is noticed. (C) Continuous wave signal showing a dense triangular signal and (D) Colour doppler flow through the tricuspid valve, both matching a severe tricuspid regurgitation grade 4/4.

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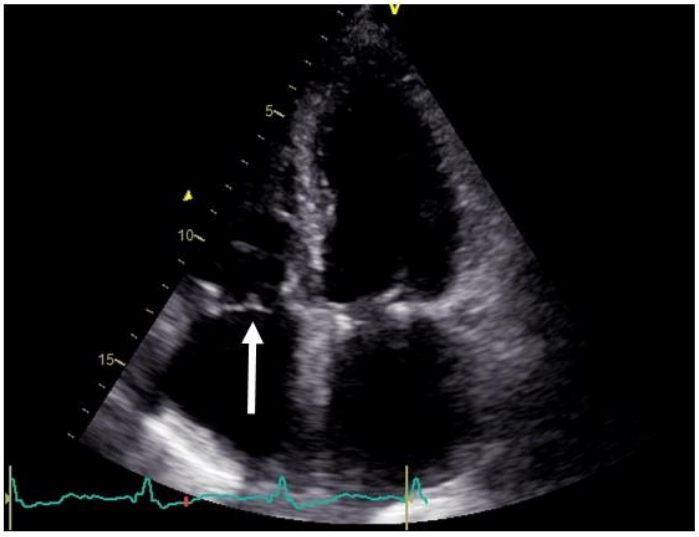

Figure 4. Transthoracic echocardiography (Apical 4-chamber view) showing postoperative status with tricuspid bioprosthesis (white arrow) properly closing during systole.

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