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ISSN 2377-164X Open Journal http://dx.doi.org/10.17140/HROJ-4-132

Case Report

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Volume 4 : Issue 1
Article Ref. #: 1000HROJ4132

Article History
Received: September 6th, 2016
Accepted: September 14th, 2016
Published: September 15th, 2016

Citation
Fernandes R, Sattiraju S, Mehta S, Ayenew W. Carcinoid heart disease and review of literature [Videos]. *Heart Res Open J.* 2016; 4(1): 1-5. doi: 10.17140/HROJ-4-132

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Carcinoid Heart Disease and Review of Literature

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ABSTRACT

Carcinoid Heart Disease (CHD) is one of the rare causes of acquired valvular heart disease. CHD develops as a systemic manifestation of metastatic neuroendocrine tumors (NETs). When these tumors metastasize to the liver, they can release vasoactive amines into the systemic circulation, which can result in carcinoid syndrome and CHD. The key for diagnosing CHD is a thorough history and physical examination supplemented with characteristic echocardiographic findings. We report a case with classic echocardiographic features of CHD, which unfolded the diagnosis of metastatic carcinoid tumor.

KEYWORDS: Carcinoid heart disease (CHD); Neuroendocrine tumors (NETs); Valvular heart disease; Carcinoid syndrome.

INTRODUCTION

Carcinoid tumors are rare neuroendocrine tumors with an incidence of 1.2-2.1% per 100,000 population per year.[1] The term "Carcinoid" generally implies well-differentiated NETs that arise from enterochromaffin cells within the gastrointestinal tract and, less commonly, in the bronchopulmonary system. The tumors often metastasize to the liver resulting in the release of vasoactive amines (serotonin, bradykinin and histamine) into the systemic circulation. The triad of cutaneous flushing, gastrointestinal hypermotility, and bronchospasm characterizes carcinoid syndrome. At diagnosis, 20-30% of cases may present with carcinoid syndrome.[2] Up to 50% of patients with carcinoid syndrome can develop CHD, which is a major cause of morbidity and mortality.[3] About 20% of cases may present as CHD at the time of diagnosis.[4] Herein, we report classic findings of carcinoid heart disease.

CASE REPORT

A 65-year-old caucasian male was referred to cardiology department for the evaluation of fatigue and dyspnea on exertion for the past four months. Additional history included spontaneous episodes of diarrhea, palpitations and non-pitting pedal edema, which were self limited. On examination, vital signs were unremarkable, but he appeared markedly flushed. Cardiovascular examination revealed a grade 2/6-holosystolic murmur heard at the left midsternal area, which intensified with inspiration. Basic laboratory investigations were unremarkable. An echocardiogram performed two weeks ago showed moderate to severe right ventricular dilation with severe right ventricular systolic dysfunction. The tricuspid valve appeared severely thickened, with its leaflets fixed in open position, giving rise to wide open tricuspid regurgitation (Figures 1 and 2).

The constellation of these signs and symptoms with classic echocardiographic findings led to a suspicion of carcinoid heart disease, which was substantiated when serum levels

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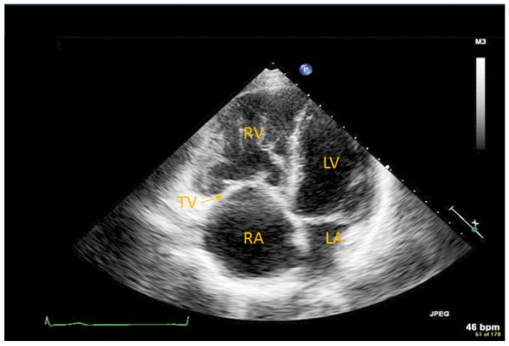
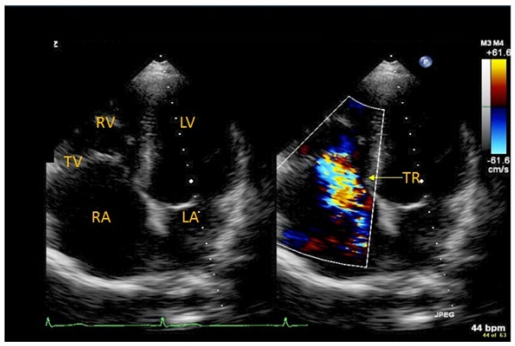


LA: Left Atrium; LV: Left Ventricle; RA: Right Atrium; RV: Right Ventricle; TV: Tricuspid Valve.

Figure 1: Apical 4 chamber view in end diastole showing severe Right atrial and ventricular enlargement. The Tricuspid leaflets are thickened and immobile (yellow arrow).



LA: Left Atrium; LV: Left Ventricle; RA: Right Atrium; RV: Right Ventricle; TV: Tricuspid Valve; TR: Tricuspid Regurgitation.

Figure 2: Immobile tricuspid leaflets with severe tricuspid regurgitation on color comparison view. Severe right atrial enlargement is noted again.

of 5-hydroxyindoleactetic acid (5-HIAA) and chromogranin-A were found to be significantly elevated.

Given severe right ventricular systolic dysfunction a computed tomography (CT) angiogram of the chest was performed to rule out pulmonary embolism (PE). The test was negative for PE, but interestingly revealed multiple heterogeneous enhancing hepatic lesions concerning for metastatic disease. The patient was then referred to Gastroenterology and subsequently underwent CT Abdomen/pelvis (Figure 4), followed by ultrasound-guided biopsy of the liver lesion.

Histopathological examination revealed a well-differentiated NETs (Figures 5, 6 and 7). An octreotide scan confirmed uptake in the multiple heterogeneous liver and abdominal masses. The patient was referred to oncology and was treated with sandostatin infusions with modest response.

The echocardiographic findings in this case are characteristic of CHD with consequent right heart failure, which explain the presenting symptoms.

DISCUSSION

Carcinoid tumors are characteristically slow growing neoplasms, commonly causing no symptoms at all until they become large or have metastasized. They have a strong propensity to metastasize, most frequently to the liver, with other sites including bones, the adrenal glands and the brain.[5] Over the past few decades the incidence of carcinoid tumors has significantly risen due to increased imaging and endoscopic evaluation.

CHD develops in the context of carcinoid syndrome due to the exposure of high levels of vasoactive substances, which induces structural changes in the cardiac valves. Although the exact pathogenesis is poorly understood, Serotonin (5-HT) has been implicated in playing a key role in valvulopathy.[6,7]

Accumulation of tissue growth factor-B latency associated peptide and a latent binding protein has been demonstrated in carcinoid heart valves.[6] 5-HT has been implicated in upregulating tissue growth factor-B, as well as stimulating collagen synthesis by heart valve interstitial cells.[7] 5-HT is metabolized

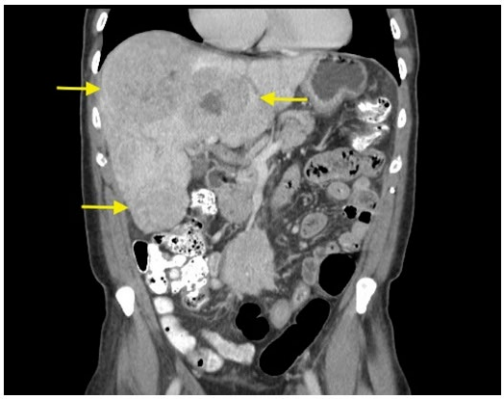


Figure 3: Computed tomography (CT) scan showing multiple carcinoid hepatic metastasis (yellow arrows).

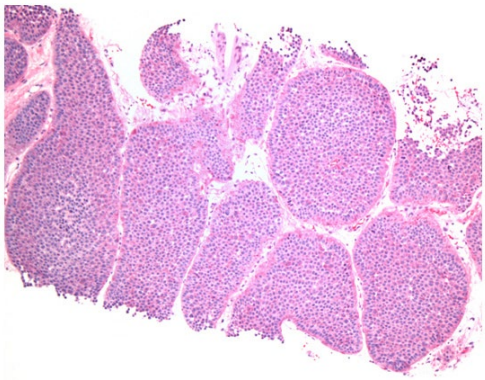


Figure 4: H&E X40: Metastatic low-grade neuroendocrine tumor arranged in nests.

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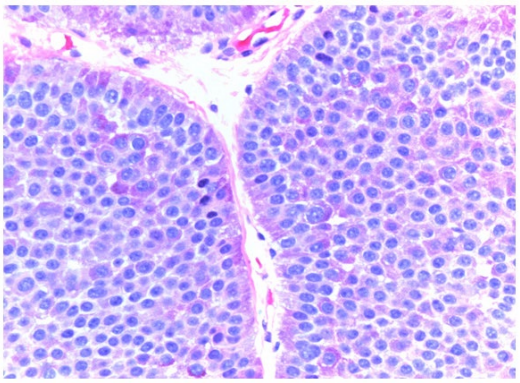

Figure 5: H&E 400: Low-grade neuroendocrine tumor showing tumor cells composed of ovoid uniform cells with inconspicuous nucleoli and stippled chromatin in moderate purplish to amphophilic cytoplasm. There is paucity of mitotic activity <2 high power focus.

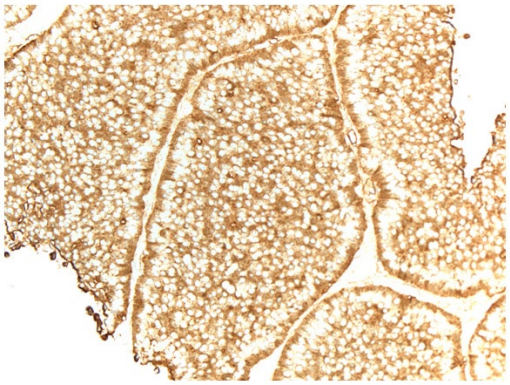

Figure 6: Chromogranin A stain of neuroendocrine tumor.

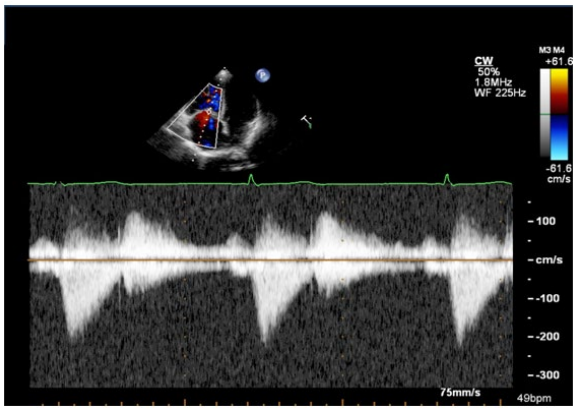

Figure 7: Continuous wave Doppler through the tricuspid valve showing severe tricuspid regurgitation with a characteristic triangular envelope due to rapid equalization of pressure between right atrium and right ventricle.

to urinary 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidases in the liver. Peak 5-HIAA is a significant predictor of progression of CHD.[8]

Typically, liver, lungs and the brain filter the vasoactive substances released from the carcinoid tumors. In the setting of liver metastases, the filtration process is bypassed resulting in release of the vasoactive substances into the systemic circulation via hepatic vein, affecting the right side of the heart in more than 90% of the cases.[3,4] The involvement of the tricuspid valve typically results in valvular regurgitation (Figures 2 and 3), and less frequently, valvular stenosis. The pulmonary valve is also effected resulting in more frequent stenosis than regurgitation, as the orifice of the pulmonic valve is much smaller, and as a consequence, plaque deposition on the pulmonary valve and within the annulus and sinuses results in narrowing of the pulmonic root. The carcinoid plaque is composed of smooth muscle cells, myofibroblasts, and elastic tissue, forming a white fibrous layer lining the endocardial surface of cardiac valves superficial to normal valve tissue.[9]

Involvement of the left side of the heart is rare accounting <10% cases, with the usual lesions being mitral or aortic regurgitation.[3,10] It can occur in the presence of patent foramen ovale with a right to left shunt, bronchial carcinoid or a very high level of circulating vasoactive substance.

The echocardiographic features of CHD have been well described in the literature.[3,11] Classically, the pulmonic and tricuspid valve leaflets and the subvalvular apparatus are thickened. The valve leaflets eventually becomes retracted, fixed, and non coapting, leading to the valve remaining in a semi-open position (Figures 1 and 2) and (Video 1).

A triangular shaped continuous wave doppler profile is seen due to severe tricuspid regurgitation, representing rapid equalization of pressures between right atrium and right ventricle due to torrential TR. (Figure 3) and (Video 2).

In most cases of CHD, the tricuspid valve with or without pulmonary valve is affected. It is the combination of right ventricular volume overload and increased diastolic filling pressures lead to hemodynamic instability.

Over the years, several novel therapies for carcinoid tumors have emerged to reduce the tumor burden and cause tumor regression. Such as, somatostatin analogues, which inhibit the vasoactive amines resulting in marked improvement in symptoms.[12]

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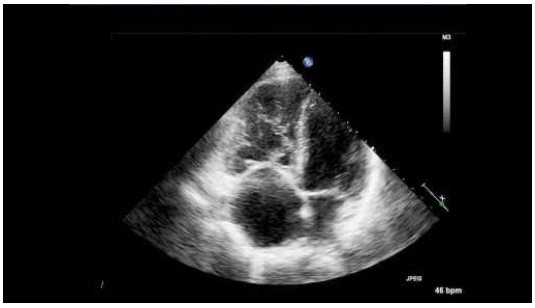
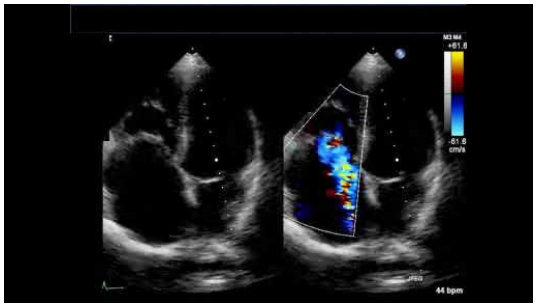


Video 1



Video 2

While medical therapy has succeeded in targeting the systemic manifestations of carcinoid syndrome, surgical therapies have targeted hepatic metastasis with embolization, resection, debulking, and liver transplant. Several studies have shown promising results in improved symptoms and longevity in patients with carcinoid syndrome.[12-16]

However, for patients with cardiac involvement, worsening right-sided heart failure remains a major cause of morbidity and mortality.

Several studies, including Moller et al, Connolly et al have shown that valve surgery is the only effective treatment and improves survival.[17,18] Without surgery, only 10% of the patients will survive after 2 years of onset of New York heart association (NYHA) functional class III and IV symptoms.[18] The optimal timing of surgery in relation to the signs and symptoms of severe valvular dysfunction has not been clearly defined. Further more, perioperative mortality for those undergoing valve replacement remains high. However, most recently Connolly et al from Mayo clinic published a large study, which looked at the early and late outcomes of surgical management in CHD.[19] The study concluded that valve operation before the onset of advanced right-sided heart failure symptoms carries a survival benefit when compared to late surgery for more advanced disease. Interestingly, the perioperative risk was also lower when treated at an experienced center by a multidisciplinary team.[19] Mechanical valve prosthesis is recommended as carcinoid involvement has been reported in porcine bioprosthesis. Therefore, symptomatic patients with CHD before the onset of advanced heart failure symptoms may benefit from early referral to valve surgery, which in turn decreases the morbidity and mortality associated with carcinoid heart disease.

CONCLUSION

In patients with carcinoid syndrome, Echocardiography is the gold standard for diagnosing CHD, given the pathognomonic appearance of the valve lesions.

Valve surgery is the only effective treatment option for patients with symptomatic CHD and has been shown to improve survival.[17] CHD warrants aggressive treatment as the disease carries high morbidity and mortality.

ACKNOWLEDGEMENT

The authors would like to acknowledge Lisa Lynn, RDCS for her expertise in obtaining echocardiogram images.

CONFLICTS OF INTEREST

The authors declare that there is no conflicts of interest regarding the publication of this paper.

CONSENT

The patient has provided written permission for the publication of this case detail.

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