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RESEARCH ARTICLE

EXOPHTALMOS REVEALING A CARCINOID HEART DISEASE: A CASE REPORT

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Abstract

Carcinoid heart disease is rare, and it is one of the primary pathologies of tricuspid and pulmonary valve. We present a 42-year-old woman who presented to our cardiology clinic with recent peripheral lower limb edema and dyspnea. Cardiac auscultation revealed a tricuspid regurgitation murmur the reason why we did the transthoracic echocardiography that demonstrated a unique right sided valvular heart disease with a morphological aspect of carcinoid heart disease. The patient has a right exophthalmos in the clinical examination that was highly suggestive of a brain tumor. So we decided to admit her in the hospital for further work up.

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Introduction:-

Carcinoid tumors are rare neuroendocrine tumors arising more commonly from the small bowel. Patients complain most commonly from carcinoid syndrome that is related to vasoactive substances release, including serotonin (5-hydroxytryptamine), 5-hydroxytryptophan, histamine, bradykinin, tachykinins, and prostaglandins. Hence, in advanced stage carcinoid heart disease can result that includes primary tricuspid and pulmonary valve pathology leading to increased morbidity and mortality due to right heart failure. In fact, the pathogenesis of the valvulopathy is not yet well understood but it is believed to be related to elevated serotonin level.

Case Report:

A 42 years old female with history of facial flushing not related to any specific episode, chronic diarrhea and protrusion of the right eye many years ago. However, her internist doctor wanted to explore the problem, but the patient refused as she was afraid. Now she presented to our clinic with recent onset of lower limb edema and worsening dyspnea in the last one week. On clinical examination, the patient was conscious oriented, right side exophthalmos, tricuspid valve regurgitation murmur and lower limbs peripheral edema. The electrocardiogram is normal.

The transthoracic echocardiography shows a preserved left ventricular ejection fraction with no left heart side valvulopathy. Severe tricuspid valve regurgitation with thickened and retracted leaflets that do not coapt with a "dagger-shaped" continuous doppler profile. The subvalvular apparatus is thickened as well. The pulmonary valve is equally thickened with moderate pulmonary stenosis and severe regurgitation. The right ventricle is dilated.

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Figure 1:- Transthoracic echocardiogram in a modified apical four chamber view showing thickened and rigid tricuspid valve leaflets in an abnormal.

This pathological aspect of the valve directed us to put the carcinoid syndrome in the differential diagnosis and hence, we decided to admit the patient in our cardiology department to do further investigations. Serum Chromogranin A (CgA) level was monitored to assess disease progression and response to therapy. The patient's CgA level was initially found to be 727 ng/mL (reference range <94 ng/mL). The 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) was elevated at 666 $\mu\text{mol}/24\text{h}$ (normal < 50 $\mu\text{mol}/24\text{h}$). Blood serotonin was also elevated at 2709 $\mu\text{g}/\text{L}$ (normal < 300) and Gastrin at 350 pg/mL (normal <121). The vasoactive intestinal peptide was elevated as well, at 144 pg/mL (normal < 101). Fine needle biopsies of the liver indicated low grade neuroendocrine tumor stage 2.

Contrast-enhanced thoracic-abdominal-pelvic CT scan shows a highly vascularised ilial mass located in the peri-umbilical region that is highly suspected to be a primary carcinoid tumor with a large mesenteric adenomegaly. Multiple hepatic masses highly vascularized suggestive of metastatic tumors. There was no pulmonary mass. The cerebral CT scan shows a bulky right sphenoid mass syndrome, suspicious and presenting a clear periosteal reaction on its external slope: probable localization secondary to the carcinoid tumor. These lesions are responsible for a subfalcorial engagement with deviation from the center line 6 mm to the left.

Cardiac MRI showed tricuspid insufficiency with moderate valve thickening in MRI and pulmonary insufficiency and stenosis. The right ventricle is dilated and not enlarged. The coronarography was strictly normal. And the RV-PA is at 26 mmHg signing a pulmonary stenosis. Octreoscan at DOPA confirms metastatic disease with hepatic delocalization and at the bone level a lesion is noted T2. We started a treatment based on octeotide derivates with somatulin: 1 injection every 28 days. The patient who presented a typical symptomatology of diarrhea with flush, improved well with the treatment with somatulin at a rate of 90 mg monthly.

There was a gradual improvement in the symptomatology, the patient was initially in anasarca and the latter disappeared with diuretics. As the response was favorable under medical treatment, we referred the patient to the university hospital center of Toulouse for multidisciplinary and more specialized follow up.

Discussion:-

Carcinoid tumors are rare, with a reported incidence of 8/100000 population [1]. It is a major cause of morbidity and mortality among patients with carcinoid syndrome. CHD has been previously described in up to 50% of patients with carcinoid syndrome [2, 3], but more recent studies suggest the prevalence has fallen to 20%. A slight male predominance has been reported (approximately 60%), with a mean age at diagnosis of 59 years [2].

The prognosis of CHD is poor if not treated. CHD with advanced symptoms (NYHA functional class III or IV) carries a particularly poor prognosis, with median survival of 11 months [4]. The median survival improved from 1.5

years in the 1980s to 4.4 years in the late 1990s thanks to increased rates of cardiac surgery and the use of somatostatin analogs.

Carcinoid heart disease is characterized by pathognomonic plaque-like deposits of fibrous tissue. These deposits occur most commonly on the endocardium of valvular cusps, leaflets, papillary muscles and cords, cardiac chambers, and occasionally on the intima of the pulmonary arteries or aorta (figure 2) [5,6].

The affected cardiac valves in carcinoid heart disease have a white appearance with thickened leaflets and subvalvular apparatus with fused and shortened chordae and thickened papillary muscles [7].

The morphology of the valve leaflet is not disrupted and the carcinoid plaque generally affects the ventricular aspect of the tricuspid valve leaflets and the arterial aspect of the pulmonic valve cusps [5, 8]. The valves and endocardium of the right side of the heart are most often affected by carcinoid disease [3, 4]; it is postulated that the left-sided valves are spared due to inactivation of humoral substances by the lung. Carcinoid plaques also commonly affect the pulmonic valve (particularly the arterial aspect) with consequent regurgitation, stenosis, or both. In patients with advanced disease, carcinoid plaque may also involve the endocardial lining of the right heart chambers. Left-sided valvular pathology occurs in less than 10 percent of patients with cardiac involvement [3]. It is almost always associated with an atrial level right-to-left shunt (as with a patent foramen ovale).

A variety of vasoactive substances secreted by the tumor, including serotonin, prostaglandins, histamine, bradykinin, and other substances with fibroblast proliferative properties, such as tachykinins (substance P, neurokinin A, neuropeptide K) or transforming growth factor-beta, are thought to be involved in the disease pathogenesis [9].

Location of fibrous plaques in carcinoid heart disease

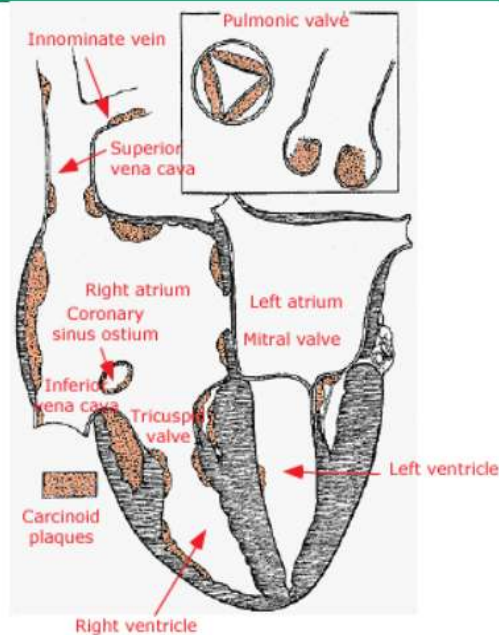


Figure 2:- In patients with carcinoid heart disease, distinctive lesions, termed carcinoid plaques, develop on the right side of the heart (tricuspid and/or pulmonic valves); such plaques are occasionally found on the left side of the heart. Adapted from Roberts WC. Am J Cardiol 1997; 80:251.

Studies suggested that serotonin plays a major role in the pathogenesis of CHD. It is well known that urinary 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite, is significantly higher in patients with CHD compared with those without cardiac involvement [9]. Furthermore, in cell culture studies, serotonin has been shown to promote cell proliferation in valvular subendocardial cells[10] and human heart valves have been demonstrated to express the serotonin receptors 5-HT_{1B}, 1D, 2A, and 2B[9,11]. Nevertheless, despite the growing evidence that

serotonin plays a major role in the development of CHD, it is likely that other biochemical mediators are also significant and may act as cofactors in the fibrotic process [12, 13].

In the early stages, CHD is usually well tolerated, hence the clinical manifestation can be subtle or absent leading to delay of diagnosis. Obvious features of flushing, diarrhea, and bronchospasm should draw attention to the possibility of the carcinoid syndrome. Physical examination reveals a systolic murmur along the left sternal edge, produced by tricuspid regurgitation; concomitant murmurs of pulmonary stenosis or regurgitation may be present [14]. The vast majority of patients with cardiac involvement present with signs of right heart failure secondary to severe dysfunction of the tricuspid and pulmonary valves. In a large US case series, 97% of the 74 patients with cardiac involvement had tricuspid valve disease, of whom 90% displayed moderate or severe tricuspid regurgitation; smaller numbers had coexistent tricuspid stenosis. Pulmonary valve pathology was noted in 88% of patients, of whom 81% had pulmonary regurgitation and 53% had pulmonary stenosis [15]. Cardiac metastases of carcinoid tumours are extremely rare. In the largest series of 11 patients derived from the Mayo clinic, carcinoid syndrome was present in all patients and all metastases were intramyocardial in location [16]. Basic screening with a 12 lead ECG and chest x ray is of limited value. Between 30–50% of ECGs are normal; nonspecific ST segment changes and sinus tachycardia are the most common abnormal findings and p pulmonale or right bundle branch block may also be seen on occasion [15,17]. The chest x ray is also largely unhelpful as around 50% are normal [15, 17]. The two key investigations for the diagnosis of carcinoid heart disease are 24 hour urinary excretion of 5-hydroxy-indole acetic acid (5-HIAA) and transthoracic echocardiography [14].

Patients with carcinoid syndrome have high concentrations of 24 hour urinary 5-HIAA. In a large series of patients with carcinoid syndrome and cardiac involvement the mean 24 hour urinary excretion of 5-HIAA was up to 10-fold higher than the reference value (reference value, 50 mmol/l per 24 hours) [15, 17]. In patients with both right and left sided carcinoid heart disease, urinary values of 5-HIAA appear to be higher in patients without interatrial shunts compared to those with interatrial shunts, suggesting greater disease activity in the former group[18].

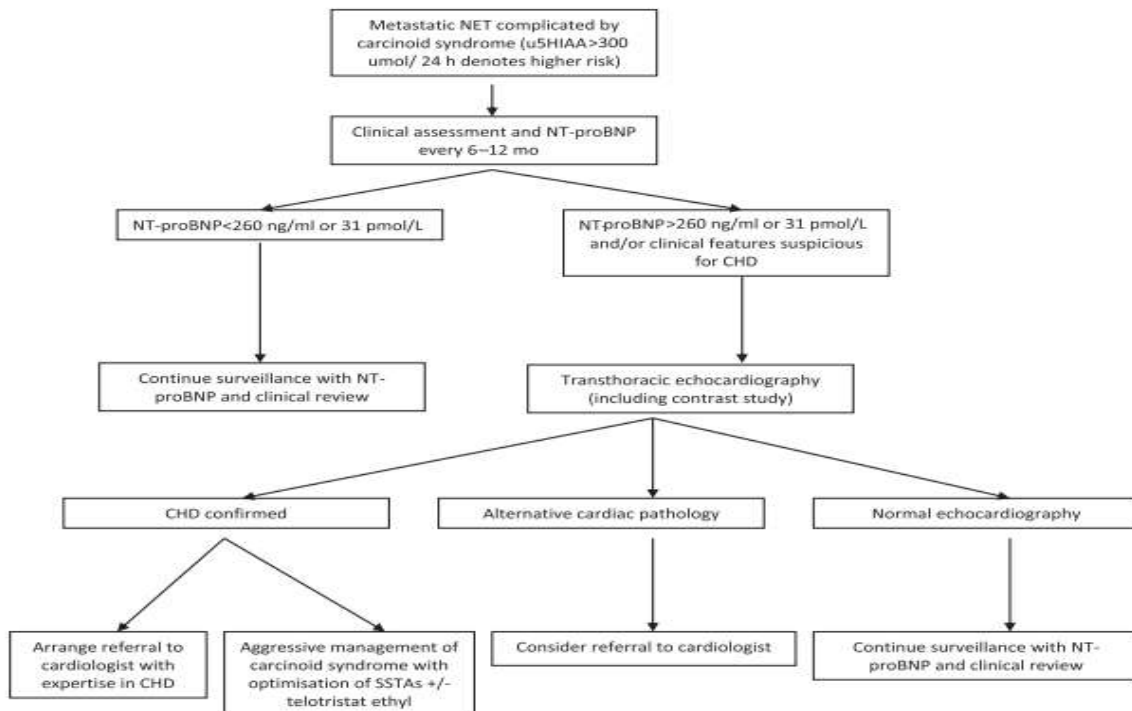


Figure 3:- Screening and evaluation of CHD. u5HIAA, urinary 5-hydroxyindoleacetic. (Adapted from Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumours. J Am Coll Cardiol 2017;69(10):1296; with permission.).

Echocardiography remains the cornerstone in the diagnosis and prognosis evaluation of carcinoid heart disease. In patients with carcinoid heart disease, right atrial and right ventricular enlargement is present in up to 90% of cases

and ventricular septal wall motion abnormalities are seen in almost half of the cases [15]. The tricuspid valve leaflets and subvalvar structures are often thickened, shortened and retracted, leading to incomplete coaptation and usually moderate or severe tricuspid regurgitation (fig 2). The continuous wave Doppler profile of tricuspid regurgitation shows a characteristic dagger shaped spectrum with an early peak pressure and rapid decline [14].

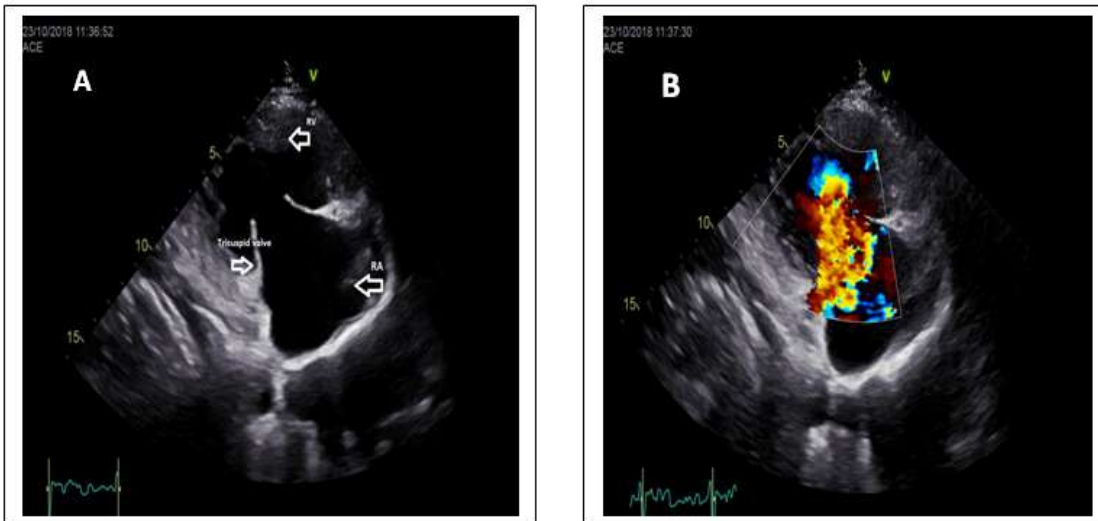


Figure 3:- (A) Transesophageal echocardiogram showing a thickened tricuspid valve with a defect of coaptation. (B) Colour flow Doppler imaging in the same view shows severe tricuspid regurgitation through a wide regurgitant orifice. RA, right atrium; RV, right ventricle.

The pulmonary valve may also be thickened and retracted, leading to pulmonary regurgitation and less commonly, pulmonary stenosis. The combination of severe tricuspid regurgitation and pulmonary stenosis is particularly problematic as this further exacerbates the tricuspid regurgitation and worsens right heart failure [14].

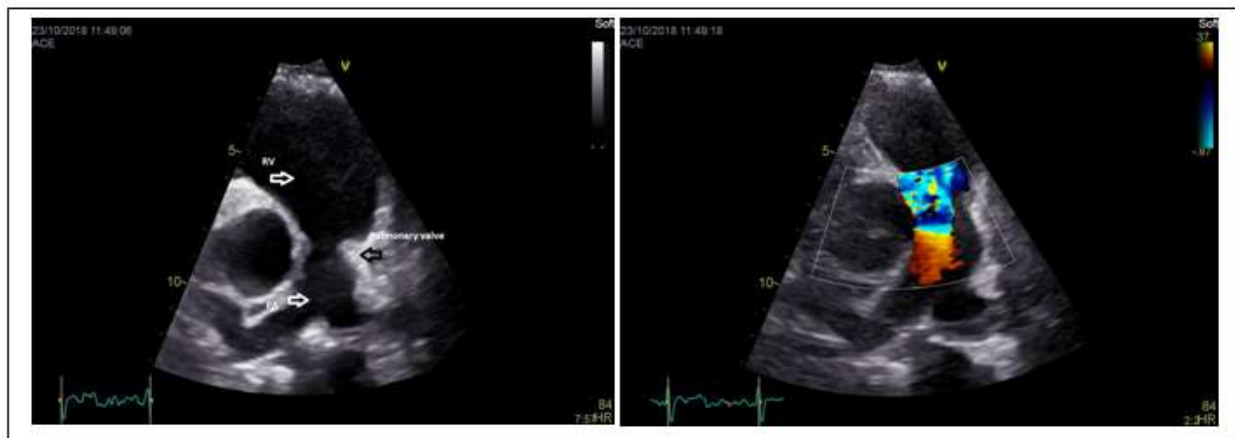


Figure 4:- (A) Transthoracic echocardiogram in a modified parasternal small axis view showing thickened and rigid pulmonary valve and stenosed. (B) Colour flow Doppler imaging in the same view shows pulmonary stenosis. PA: pulmonary artery; RV: right ventricle.

Transesophageal echocardiography may provide incremental assessment of the degree of cardiac valve involvement and the atrial septal anatomy in patients with carcinoid heart disease. Since the right-sided valves are in the far field, assessment by TEE is less reliable than assessment of left-sided valves, but an experienced examiner is usually able to obtain diagnostic images of the right-sided valves [19]. CT or MRI allows delineation of valve pathology, assessment of valve regurgitation and stenosis, and may be particularly helpful for quantification of ventricular

volumes [20]. MRI also allows assessment of myocardial metastases, including measurement of size and extracardiac invasion that cannot be assessed on echocardiography [20].

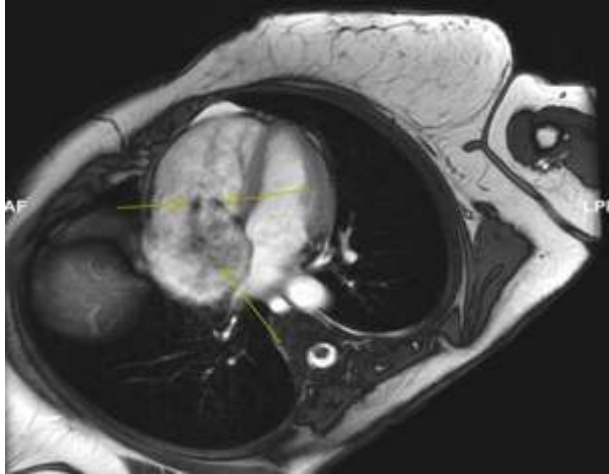


Figure 5:- An axial CMR image through the heart shows thickened leaflets of the tricuspid valve with regurgitation (arrowheads) and an enlarged right atrium with a bulging interatrial septum (arrow) reflecting elevated right atrial pressures in our patient.

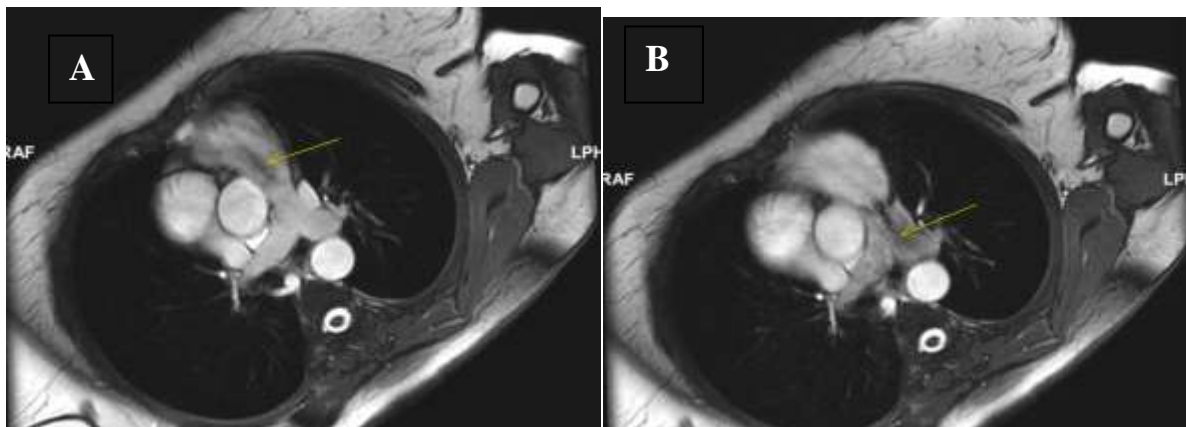


Figure 6:- (A) An axial CMR image through the pulmonary artery shows a pulmonary regurgitation (arrow). (B) In the same view: pulmonary stenosis with flow acceleration in the pulmonary tract.

General measures for the treatment of heart failure include salt and water restriction. Right heart failure can be successfully treated with a combination of loop diuretics and digoxin, the judicious coadministration of a thiazide diuretic usually produces the desired effect [21]. The use of somatostatin analogues has been noted to provide symptomatic improvement and improved survival in patients with carcinoid heart disease [14]. Treatment with octreotide gives rise to both directly observable clinical benefit and measurable biochemical improvement [14]. About 70% of patients obtain symptomatic relief from diarrhoea and flushing, showing a decrease in measurable 5-HIAA urinary secretion and serum 5-HT concentrations [22]. Addition of IFN- α , or peptide receptor radionuclide therapy (PRRT) in case of refractory carcinoid syndrome may be useful. The oral serotonin synthesis inhibitor, telotristat, represents a promising agent to improve symptoms of the carcinoid syndrome.

Valve surgery (tricuspid valve replacement with addition of pulmonary valve replacement in patients with pulmonary valve disease) is the only approved intervention for carcinoid heart disease [19]. Valve surgery is an option only for patients whose metastatic carcinoid disease and symptoms of carcinoid syndrome are well controlled [19]. The choice of valve prosthesis should be individually tailored on the basis of the patient's bleeding risk, and possible future therapeutic interventions. Biological valve prostheses are the preferred option (Evidence Level 4, Grade D) [23]. To prevent a carcinoid crisis during surgery, the patient should be started on an IV octreotide infusion at a rate of 50-100 mcg/h at least 12 hours preoperatively; this should be continued throughout the procedure and until stable. Patients should be monitored for occurrence of bradycardia if high doses of octreotide are

used (Evidence Level 4, Grade C) [23]. The patient with carcinoid heart disease should be managed by a specialized multidisciplinary team, within a setting of a specialized neuroendocrine tumor (NET) center [23].

In the last decade, the prognosis of CHD has significantly improved thanks to medical treatment and the evolution of surgery. However, those over the age of 60 years are considered to have a high surgical mortality, with one study quoting a 63% death rate [24] possibly even higher in patients with significant co-morbidity.

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