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(CASE REPORT)

Heidinger syndrome - Carcinoid syndrome

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Abstract

Carcinoid heart disease was first described in 1954. It develops in over 70% of carcinoid syndrome patients. Up to 20% of patients with carcinoid syndrome have pronounced carcinoid heart disease at diagnosis. Cardiac involvement is usually well tolerated by patients. Symptoms are associated with secretion of serotonin, tachykinin and other vasoactive substances in the systemic circulation. Deposition of fibrous tissue along the tricuspid annulus leads to ring constriction and is the basis of tricuspid stenosis. Primary insular carcinoid tumor of the ovary is a very rare tumor that accounts for less than 1% of all carcinoid cases.

We present a case of a 62-year-old woman, demonstrating shortness of breath and fatigue, diarrhea, redness and progressive swelling on both lower legs. After single-photon emission computed tomography we found pathologically increased somatostatin expression in a tumor formation in the pelvis. After removal of the primary focus, the patient received a prosthetic tricuspid valve with good clinical results.

Keywords: Carcinoid; Tricuspid valve stenosis; Tricuspid regurgitation.; Serotonin; Tachykinin.

1. Introduction

William Ransom reported the first case of carcinoid syndrome in 1890. The patient was a 50-year-old woman with diarrhea and wheezing in the lung, presenting later with multiple intestinal and liver tumors. The term "carcinoid" was first used by Oberndorfer in 1907 to define adenocarcinoma with a benign course. Although these neoplasms were initially considered benign, their malignant potential is now well known [1]. In 1948 Rapport et al. isolated the substance serotonin (5-HT), which has been shown to be responsible for the development of this syndrome [2].

Carcinoid tumors are relatively rare neuroendocrine neoplasms, most often originating from enterochromaffin cells of the gastrointestinal tract [3].

Carcinoid heart disease was first described in 1954 [4]. It develops in over 70% of carcinoid syndrome patients [5,6]. Development of symptoms is associated with vasoactive substances secreted by metastatic tumor cells in the liver, thus surrounding the portal system and reaching the right heart. This results in deposition of fibrous tissue on the endocardial surface of the heart. Recently, there has been a decrease in the incidence of cases with these manifestations. This may be due to the already available somatostatin analogues and other antitumor therapeutics designed to reduce tumor load and reduce tumor-secreted substances [7]. As an exception, carcinoid heart disease can develop in carcinoid

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tumor without affecting the liver from metastasis, e.g. in primary ovarian carcinoid tumors, where 5-HT reaches the systemic circulation, initially bypassing the portal venous system.

Up to 20% of patients with carcinoid syndrome have pronounced carcinoid heart disease at diagnosis. Cardiac involvement is usually well tolerated by patients. In most cases, NYHA functional class I is established despite significant morphological changes in the right heart. As the disease progresses, symptoms of shortness of breath on exertion, swelling around the ankles and fatigue may occur.

2. Clinical manifestation

The clinical manifestation of carcinoid syndrome is the result of metastasis of cells to the liver or primary localization, surrounding the portal system. Symptoms are associated with secretion of serotonin, tachykinin and other vasoactive substances in the systemic circulation. As a result of these hormones, there is manifestation of diarrhea, redness, rhinorrhea, lacrimation and palpitations. In the presence of cardiac involvement, a holosystolic murmur of tricuspid regurgitation (TR) is found, as well as a systolic murmur of pulmonary stenosis along the left sternal edge. The noise findings are difficult to establish due to relatively lower velocities and pressures in the right heart cavities. Peripheral edema, ascites, and hepatomegaly develop as the disease progresses.

3. Biochemical markers and pathogenesis of carcinoid heart disease

The pathogenesis of the disease and development of connective tissue deposits are not yet fully understood in detail, but there is evidence for the key role of serotonin (5-HT). The thesis of 5-HT induced valvulopathy is based on several recent studies. The appetite suppressant drugs fenfluramine and phenteramine were withdrawn from the market due to the development of valvular pathology after their use. The morphological change in the affected valve leaflets is identical to that observed in carcinoid heart disease [8]. 5-HT has been shown to increase synthesis of tissue growth factor beta (TGF-β) and to activate collagen synthesis by interstitial cells in the valve leaflets [9]. The presence of 5-HT receptors in the heart valves explains the pathophysiology of their involvement in carcinoid heart disease.

In animal models, long-term exposure to 5-HT and the absence of the 5-hydroxyindoleacetic acid (5-HIAA) transporter gene induced morphological and echocardiographic changes, which were identical to observed cardiac fibrosis and valvulopathy in carcinoid heart disease [10, 11].

4. Morphological and histological characteristics of carcinoid heart disease

The carcinoid plaque consists of smooth muscle cells, myofibroblasts, and elastic fibers that form fibrous sheaths covering the endocardial surface of the heart valves. Native valve structures and morphology located beneath these sheaths remain unaffected [12]. these plaques and deposits develop on the endocardium of the valves, subvalvular apparatus, right atrium, and right ventricle. Similar fibrous deposits have been found in the inferior vena cava, pulmonary artery and its branches, coronary sinus and even in coronary arteries [13]. Tricuspid valve involvement has fibrous deposits on the ventricular surface of the leaflet, leading to retraction and adhesion to the mural myocardium, which is the substrate of significant tricuspid regurgitation. Deposition of fibrous tissue along the tricuspid annulus leads to constriction of the ring and is the basis of tricuspid stenosis. Involvement of the pulmonary valve is in the direction of stenosis due to constriction by fibrosis of the root of the pulmonary artery and realization of a smaller valve opening [14].

5. Primary ovarian carcinoid tumor

Primary insular carcinoid tumor of the ovary is a very rare tumor that accounts for less than 1% of all carcinoid cases. Almost all the described cases so far have a diameter of less than 10 cm [15].

Histological analysis of carcinoid tumors divides them into insular, trabecular and strumal with and without a dermoid component. Insular carcinoids are the most common. [16]. Analysis of Soga J et al. showed a difference in the groups with and without cystic teratoma or dermoid involvement. Those with a dermoid component are significantly smaller, less likely to metastasize, less likely to affect the liver, less likely to develop carcinoid syndrome, and have better survival [17].

6. Clinical case

A 62-year-old patient was admitted with complaints of shortness of breath and fatigue in normal exertion, diarrhea 3-4 times a day, redness and progressive swelling on both lower legs.

Echocardiographical examination showed: preserved LV pump function, symmetrical kinetics; slightly dilated RV with preserved systolic function and higher volume load; TAPSE 20 mm, mean diastolic gradient through the tricuspid valve 4.5 mmHg, high-grade regurgitation. The tricuspid valve leaflets were opturated without coaptation. (Fig.1)

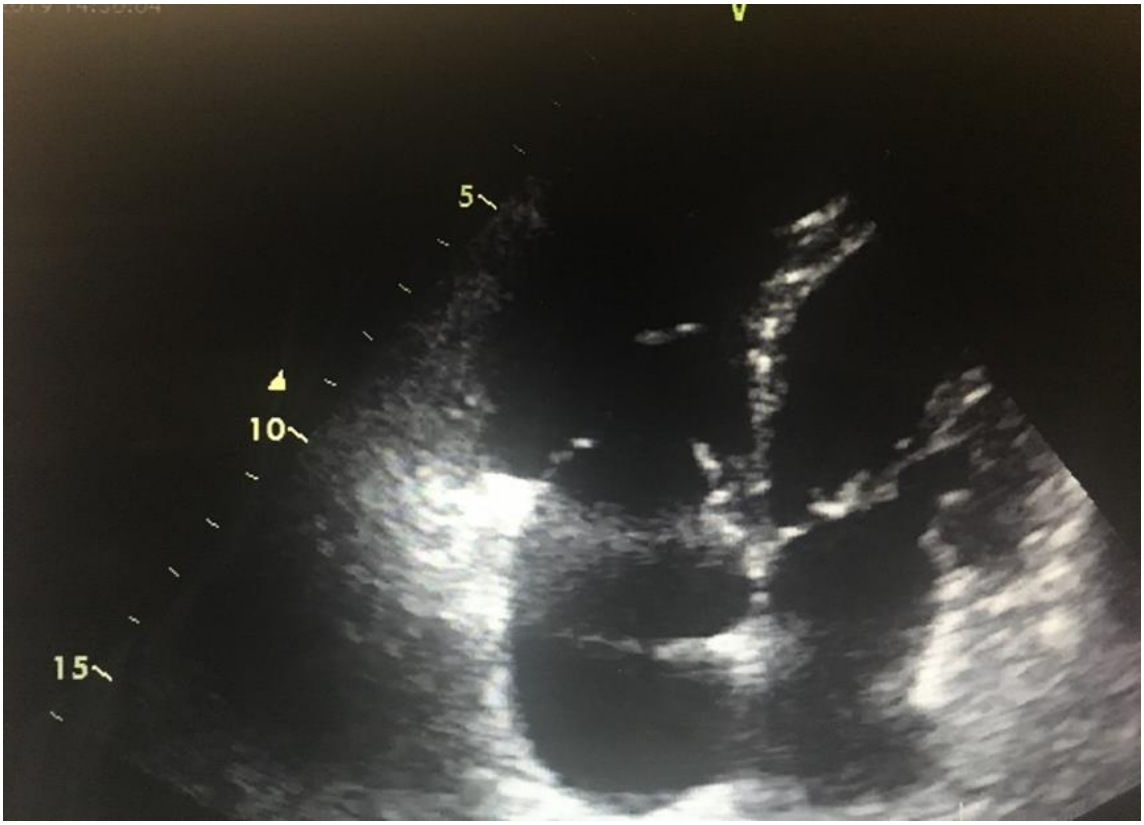

Figure 1 Echocardiography- The tricuspid valve leaflets were opturated without coaptation.

Due to suspicion for carcinoid, she was referred for right heart catheterization (RHC) to the St. Anna University Hospital, Sofia in June 2018. The conducted invasive examination revealed RV dilatation and hypertrophy, IV degree tricuspid regurgitation, high RA pressure and small gradient of the pulmonary valve. During hospital stay she was consulted by a gastroenterologist and an obstetrician-gynecologist. Ultrasound of abdominal organs revealed a tumor formation in the small pelvis. A soft tissue lobulated formation with pathological density (dimensions in the axillary plan - 57/64 mm, sagittal plan - 80/60 mm and coronary plan - 85/73 mm) was established from a CT scan performed on a dorsal contour of the uterine body.

The patient was referred to the Clinic of Nuclear Medicine - Sofia, where SPECT CT was performed and found: pathologically increased expression of somatostatin receptors in a tumor formation in the pelvis at the described location (above the uterus and bladder, dorsally at the level of L5/S2 and suspected central necrosis. (Fig. 2)

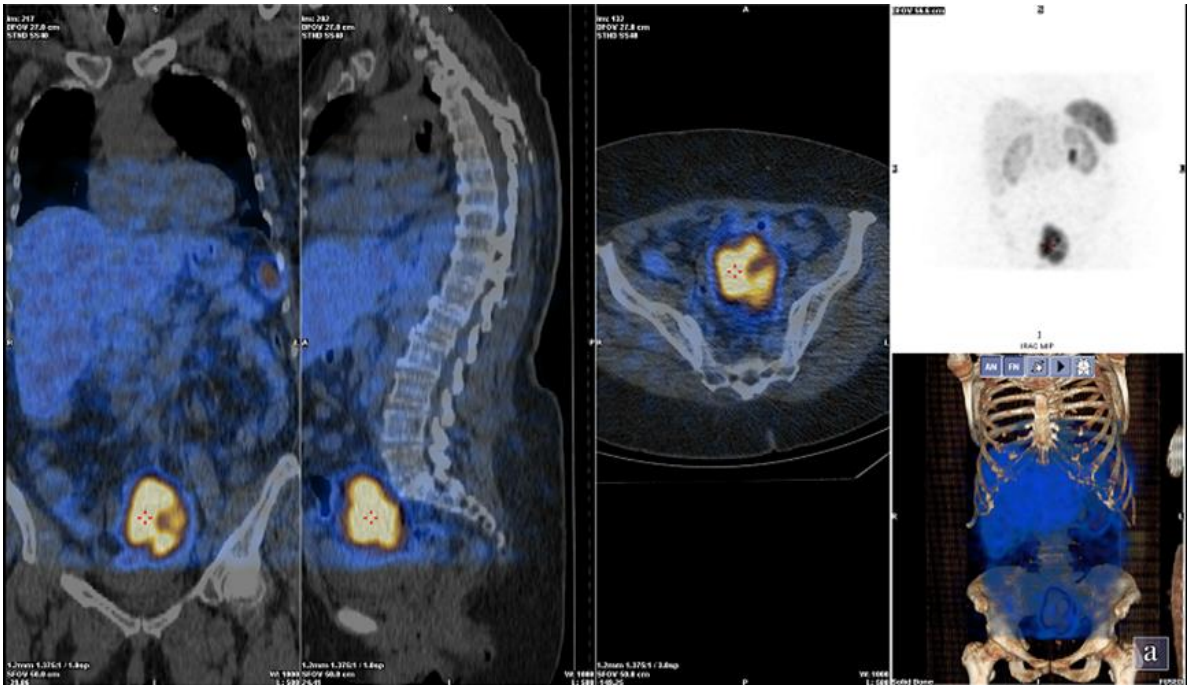

Figure 2 SPECT CT - data on pathologically increased expression of somatostatin receptors in a tumor formation

In July 2018, the patient was hospitalized at the Hospital of Obstetrics and Gynecology, Sofia for total hysterectomy with bilateral adnexectomy. Due to frozen section procedure data for adenofibroma on the left adnexa, partial omentectomy was also performed.

Histological results showed:

- Uterine body - cystic atrophic endometrium. Cervix - focal metaplastic squamous epithelium with groups of atypical koilocytes;
- Left ovary - insular carcinoid (immunohistochemical examination).

At the follow-up examination 3 weeks after the surgical treatment, the complaints of flush and diarrhea have disappeared. Swelling persisted, but were significantly reduced and controlled with diuretic treatment.

In the beginning of August 2018, the patient presented with swelling of the right arm, starting from the shoulder, with a developed visible venous collateral network along the anterior chest wall. Contrast venography visualized thrombosis involving the axillary vein and right subclavian vein. Anticoagulant therapy with rivaroxaban 20 mg/d was initiated. After 40 days of treatment, reversal of the edema and reduction of the venous collateralization was observed. After 3 months, control venography showed permeable venous system of the right upper limb and anticoagulant treatment was discontinued. Venous thrombosis was associated with previous hospitalization and reactive thrombophlebitis of the right cubital vein.

In December 2018 the patient was targeted for PET CT due to high level of tumor marker Ca 125-408IU/ml. The PET CT of the whole body with 6.2 mCi 18F-FDG revealed anscence of metabolically active zones that could be directly associated with recurrences or secondary lesions. Presence of ascites and pleural effusion on the right was found.

The patient was indicated for surgical treatment of the tricuspid valve defect. For this purpose, control RHC was performed. Recorded pressures at rest were: right atrium 28/35/26 mmHg; pulmonary artery 39/21/27 mmHg; left ventricle 147/10 mmHg, telediastolic LV pressure 28 mmHg; aortic pressure 141/90/114 mmHg

Right ventriculography showed: LV dilatation and hypertrophy, III-IV degree tricuspid regurgitation, extremely high LA pressure.

In February 2019, tricuspid valve prosthesis was performed. The intraoperative findings showed thickened leaflets of the tricuspid valve and advanced fibrosis of the subvalvular apparatus. The valve had total destruction and missing coaptation surface. Measured valve annulus > 40 mm. In order to preserve the subvalvular apparatus and, respectively, LV geometry, a biological prosthesis with a diameter of 33 mm was implanted by the "valve-in-valve" method, without compromising the AV node area and LV outlet tract. (Fig. 8) The patient was discharged on March 11th, 2019 in stable sinus rhythm without complaints of shortness of breath or other discomfort.

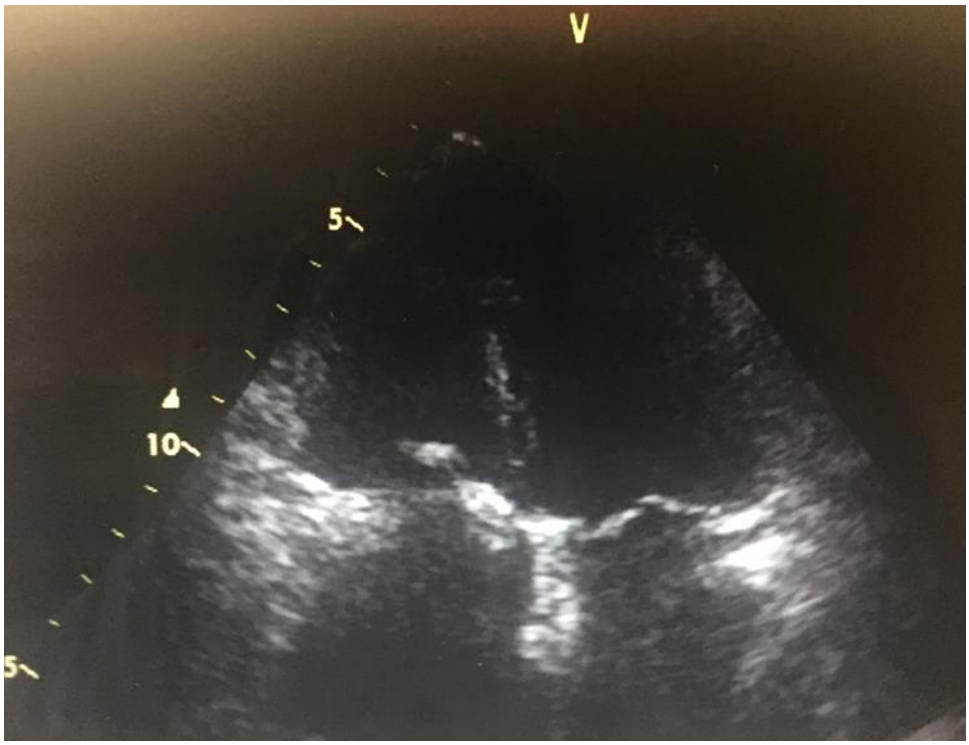

Figure 3 A biological prosthesis of tricuspid valve

In the early postoperative period, atrial fibrillation paroxysm with high-frequency ventricular response was registered. Due to unsuccessful attempts to recover sinus rhythm, we decided to adopt a heart rate control strategy.

After 6 months, the patient was diagnosed with an eventration of the anterior abdominal wall in the area of the operative scar. After consultation with a surgeon, conservative treatment was recommended due to the high operative risk to the cardiovascular wall. Due to clinical data for incarceration of intestinal loops and subileus in February 2021, she underwent emergency surgery with subsequent plastic surgery with polypropylene mesh in retrorectal position. The postoperative period was without complications.

7. Discussion

Carcinoid heart disease is a relatively rare disease that can lead to patient disability and fatal consequences. Symptoms and manifestation depend exclusively on the location of the primary tumor. In the described clinical case, symptoms demonstrated relatively early, due to a primary focus that surrounded the portal vascular system. Timely diagnosis allowed for adequate treatment and stabilization of the patient's condition.

8. Conclusion

Clinical manifestation of tricuspid valve stenosis and absence of rheumatoid heart disease should lead to deeper investigation. Carcinoid heart disease diagnosed early is treatable and long-term prognosis for the patient is relatively good.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest.

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The authors declare that there is no conflict of interests regarding the publication of this paper.

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