

Carcinoid syndrome with right-sided valve involvement – a case report and review of the literature

Postižení pravostranných srdečních chlopní u pacientky s karcinoidovým syndromem – kazuistika a přehled literatury

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Summary

Background: The survival of patients with neuroendocrine tumors has substantially improved with modern treatment options. Although the associated carcinoid syndrome can be diagnosed early and controlled effectively, cardiologists still encounter patients with cardiac manifestations, particularly among individuals with persistently high levels of vasoactive mediators. Treatment options have been limited to surgical valve replacement in fully manifested disease. Since surgery is not always feasible, transcatheter valve implantation is becoming an interesting alternative. **Case:** A case of a 50-year-old woman with carcinoid syndrome and right-sided valvular heart disease is presented. Moderate pulmonary valve stenosis and severe tricuspid valve regurgitation were diagnosed during the evaluation and treatment of neuroendocrine tumor. The possibility of rare valve involvement and the need for interdisciplinary cooperation in the diagnosis, monitoring and treatment of patients with neuroendocrine tumors producing vasoactive substances must be emphasized. **Conclusion:** The patient had a typically presenting carcinoid syndrome with a rare cardiac manifestation. Although monitoring and treatment were carried out in accordance with recommendations and appropriate to the clinical condition, rapid progression of the metastatic disease ultimately precluded invasive cardiac intervention.

Key words

neuroendocrine tumor – malignant carcinoid syndrome – carcinoid heart disease – tricuspid valve insufficiency – pulmonary valve stenosis

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Souhrn

Východiska: Přežití pacientů s neuroendokrinními nádory se výrazně zlepšilo s použitím moderní onkologické léčby. Asociovaný karcinoidový syndrom může být časně diagnostikován, přesto se stále můžeme setkat s jeho kardiální manifestací, zvláště pak u jedinců s přetrvávajícími vysokými hladinami vazoaktivních mediátorů. Léčebné možnosti u plně vyjádřeného kardiálního postižení bývaly limitovány na chirurgickou náhradu chlopní, která není vždy proveditelná. Transkatetrové chlopní intervence se proto stávají zajímavou alternativou k operačním metodám. **Případ:** Prezentujeme případ 50leté pacientky s karcinoidovým syndromem a postižením pravostranných srdečních chlopní. Během evaluace neuroendokrinního nádoru byla diagnostikována středně těžká pulmonální stenóza a těžká trikuspidální regurgitace. Detailně je popsáno vzácně se vyskytující chlopní postižení a zdůrazněna nutnost mezioborové spolupráce při diagnostice a léčbě neuroendokrinních tumorů s produkcí vazoaktivních substancí. **Závěr:** U pacientky byla vyjádřena velmi vzácná kardiální manifestace karcinoidového syndromu. Ačkoliv léčba byla vedena v souladu s platnými doporučeními a s ohledem na aktuální klinický stav, rychlá progresse metastatického onemocnění nakonec znemožnila zvažovanou invazivní chlopní intervenci.

Klíčová slova

neuroendokrinní nádor – maligní karcinoidový syndrom – karcinoidové srdeční onemocnění – trikuspidální insuficience – stenóza pulmonální chlopně

Introduction

Neuroendocrine tumors (NETs) occur sporadically or rarely in a familial form with the necessity of regular family screening [1]. Carcinoid heart disease (CHD) is a rare condition that may accompany NETs with carcinoid syndrome (CS). The symptoms characteristic of CS include chronic secretory diarrhea and skin flushing as well as bronchospasms or abdominal pain. These symptoms are caused by systemically increased levels of serotonin and/or other biologically active amines and peptides. In the case of cardiac involvement, fibrous deposits are formed on the valves and the endocardium. Right-sided heart valves are predominantly affected. The prevalence of CS in patients with NETs range of 19–35%, and CHD is present in approximately 20–50% of patients with CS. CHD remains the principal prognostic factor that reduces overall 3-year survival (31 vs. 69% in CHD vs. non-CHD patients, respectively) [2].

Case report

A 50-year-old woman was examined for dyspeptic syndrome consisting of diarrhea lasting 3 years. The patient had no major comorbidities and had never been seriously ill. She suffered from episodic flushing involving the face and upper chest. Physical examination revealed a loud systolic murmur.

The patient was examined by a gastroenterologist with negative findings. Endoscopy did not confirm any structural abnormalities. Initial laboratory test re-

sults were normal, including mineral and glucose concentrations, kidney and liver tests, blood count and coagulation test. Multiple liver metastases were shown by

ultrasound imaging; therefore, an abdominal computed tomography scan was performed. Disseminated malignant process was highly probable, so the

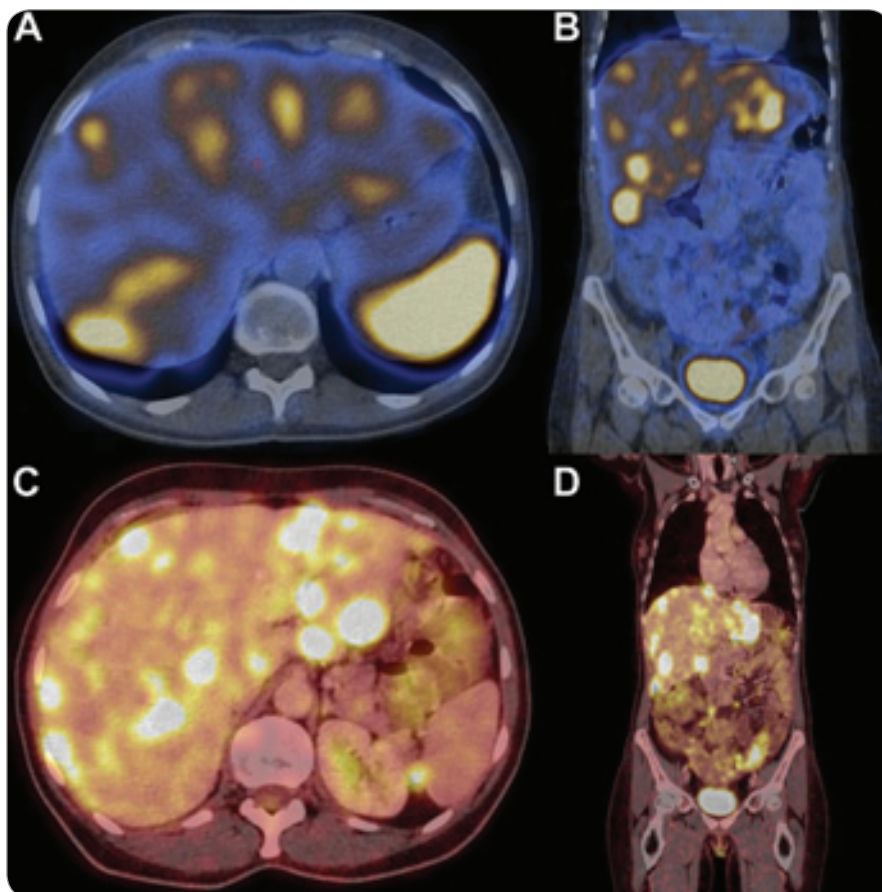


Fig. 1. SPECT/CT and PET/CT imaging. Multiple liver metastases of neuroendocrine tumor. A) Tektrotyd scan, transversal plane, SPECT/CT showing an intense Tektrotyd uptake in the liver metastases; B) Tektrotyd scan, coronal plane, SPECT/CT showing an intense Tektrotyd uptake in the liver metastases; C) PET/CT showing ^{18}F -fluorodeoxyglucose accumulation in the liver metastases, transversal plane; D) PET/CT showing ^{18}F -fluorodeoxyglucose accumulation in the liver metastases, coronal plane.

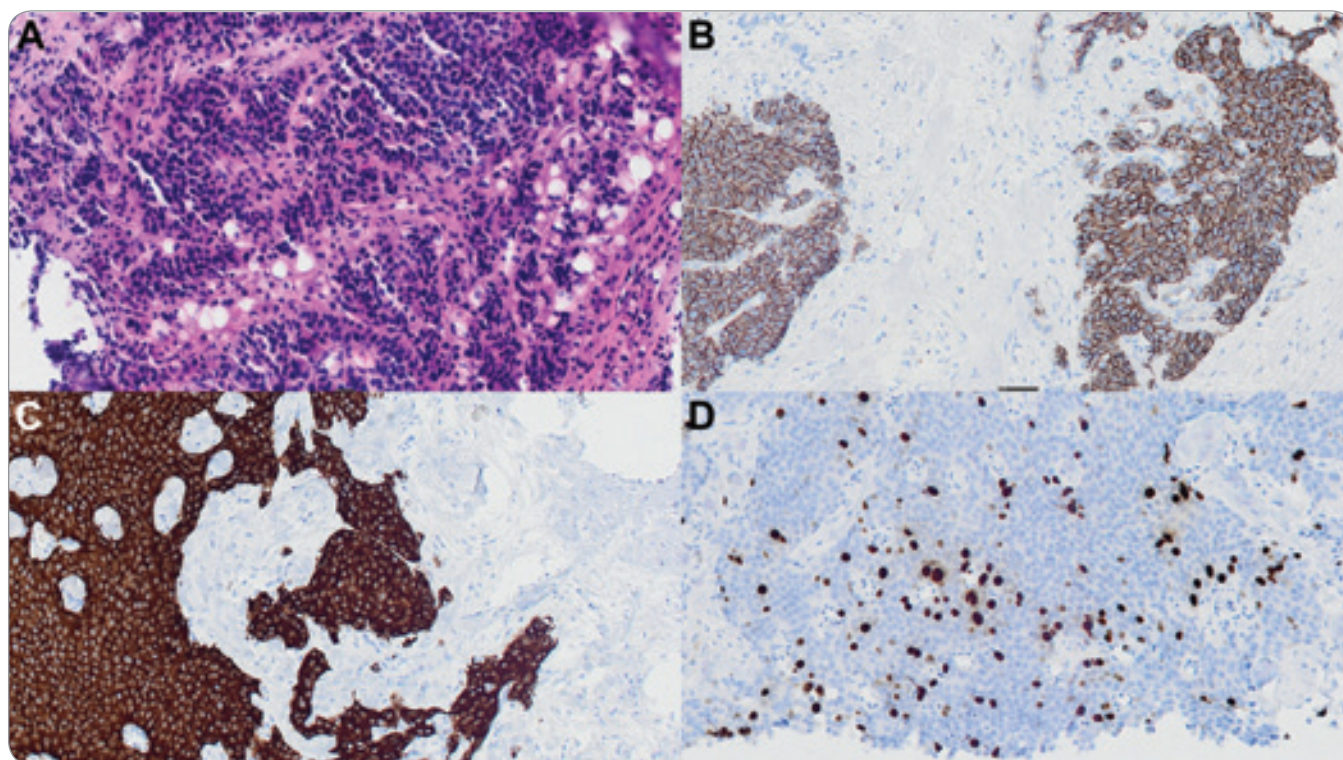


Fig. 2. The neuroendocrine tumor grade 2 in the liver biopsy. A) Hematoxylin-eosin staining; B) positive CD56 immunohistochemistry; C) positive synaptophysin immunohistochemistry; D) increased proliferation index Ki67.

next diagnostic step was PET/CT. Multiple lesions of ^{18}F -fluorodeoxyglucose uptake were detected by PET/CT imaging (Fig. 1).

Histologic and immunohistochemistry examinations were performed after successful CT-guided liver biopsy. The diagnosis of NET grade 2 was confirmed (Fig. 2). The serum chromogranin A level was significantly elevated. There was also a slight increase in serum neuron-specific enolase. Multiple lesions expressing somatostatin receptors were confirmed by Tektrotyd scintigraphy (Fig. 1). The primary site remained unclear, although the gastrointestinal tract was considered likely.

The patient was started on somatostatin analogs (SSAs); 120 mg of lanreotide was administered subcutaneously every 28 days. Even though natriuretic peptide levels were not increased, echocardiography was performed. Moderate pulmonary valve (PV) stenosis and moderate tricuspid valve (TV) regurgitation were revealed. There was no right ventricular (RV) dilatation or dysfunction (Fig. 3). The patient had no symptoms of

heart failure. A conservative approach with echocardiography follow-up was primarily decided by a multidisciplinary team consisting of a cardiologist, a cardiac surgeon, an anesthesiologist and a medical oncologist.

Six months later, the condition of the patient deteriorated rapidly. The patient had signs of fluid retention with lower limb edema, ascites, with progression to anasarca. Laboratory tests revealed kidney and liver dysfunction. The serum chromogranin A level increased significantly. PET/CT showed metastatic disease progression. Natriuretic peptide elevation was confirmed. Echocardiography demonstrated RV dilatation and diastolic D-shaped left ventricle. Severe TV regurgitation was noted. The TV leaflets were thickened with a significant coaptation defect (Fig. 4). Pulmonary stenosis remained moderate, and mild pulmonary, mitral and aortic regurgitation was also detected. Transesophageal echocardiography was planned for further valve evaluation and exclusion of right-to-left shunt, but the patient condition deteriorated rapidly, even-

tually leading to death. The patient died 8 months after the first evaluation of carcinoid heart disease, apparently due to the progression of metastatic disease with liver and renal dysfunction. The contribution of right-sided heart failure could not be excluded.

Discussion

The term carcinoid heart disease denotes cardiac manifestations in patients with CS who develop TV and PV regurgitation or stenosis, and commonly right-sided heart failure. In the presence of a right-to-left shunt, left-sided valves may be involved. Carcinoid syndrome occurs when the liver cannot inactivate vasoactive substances, as in the case of liver metastases. In 5% of cases, CS may develop without liver involvement if the vasoactive substances are released directly into the systemic circulation, as in ovarian NETs, retroperitoneal metastases, or lung NETs [3].

In the present patient, the PV and TV were simultaneously involved. Multiple liver metastases could deliver vasoactive substances directly into the systemic

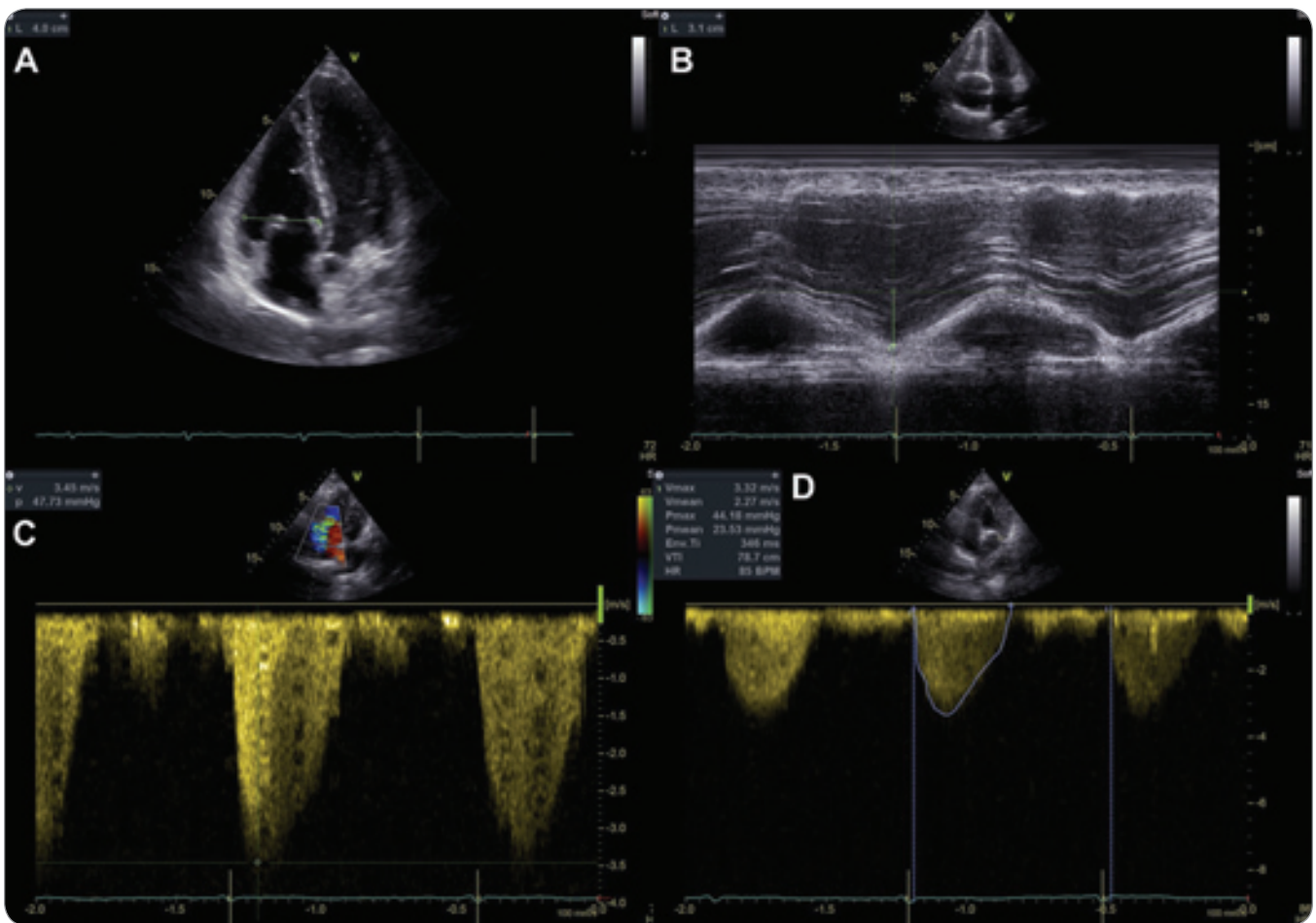


Fig. 3. Transthoracic echocardiography at baseline. A) Non-dilated right ventricle and atrium in the apical four-chamber view, the tricuspid valve with thickened and restricted leaflets; B) normal tricuspid annular plane systolic excursion; C) continuous wave Doppler profile of moderate tricuspid regurgitation; D) continuous wave Doppler profile of moderate pulmonary stenosis.

circulation. The patient suffered from CS for 3 years. High levels of vasoactive substances have damaged the endocardium long enough to develop valvular lesions.

It is important not to underestimate a careful physical examination and history. CS with cardiac involvement should be considered in the presence of diarrhea, flushing and heart murmur. Elevated natriuretic peptide levels may indicate possible cardiac involvement. N-terminal pro-B-type natriuretic peptide levels should be optimally assessed every 6 months with a cut-off value of 260 pg/mL [3]. In the present case, natriuretic peptide levels were measured twice in 6 months, and only the second measurement showed an elevation. However, moderate TV regurgitation and PV stenosis were already present when the first sample was ob-

tained. Natriuretic peptides are elevated in heart failure syndrome when it may be too late for valve replacement. In all patients with CS, cardiac imaging should be considered on a regular basis.

Because of the availability and non-invasive nature, transthoracic echocardiography is the mainstay of diagnostic evaluation. Tricuspid valve involvement is the most common CHD manifestation [4]. The leaflets are diffusely thickened, retracted and fail to close in systole, leaving an often sizeable central gap. There is incomplete opening in diastole, limited leaflet mobility, and loss of leaflet pliability. These abnormalities lead to the development of severe TV regurgitation in full-fledged disease.

Although extremely rare, TV stenosis should also be looked for [5].

The morphological characteristics of the TV were consistent with primary car-

cinoid involvement in the patient, as was the coexistence of moderate PV stenosis. In the present case, the severity of TV insufficiency progressed over 6 months and right-sided heart failure manifestations developed. Right-sided heart dilatation occurred, but without RV dysfunction (Tab. 1). Rapid CHD worsening was associated with tumor progression. Kidney and liver dysfunction may have contributed to fluid retention and RV volume overload. Hydronephrosis was present in the terminal stage of the disease. The desmoplastic potential of serotonin induces retroperitoneal fibrosis and may be involved in the pathophysiology of hydronephrosis [6]; compression by metastases adjacent to the left kidney could also play a role. The progression of liver metastases apparently contributed to liver dysfunction. In contrast, heart failure could lead to im-

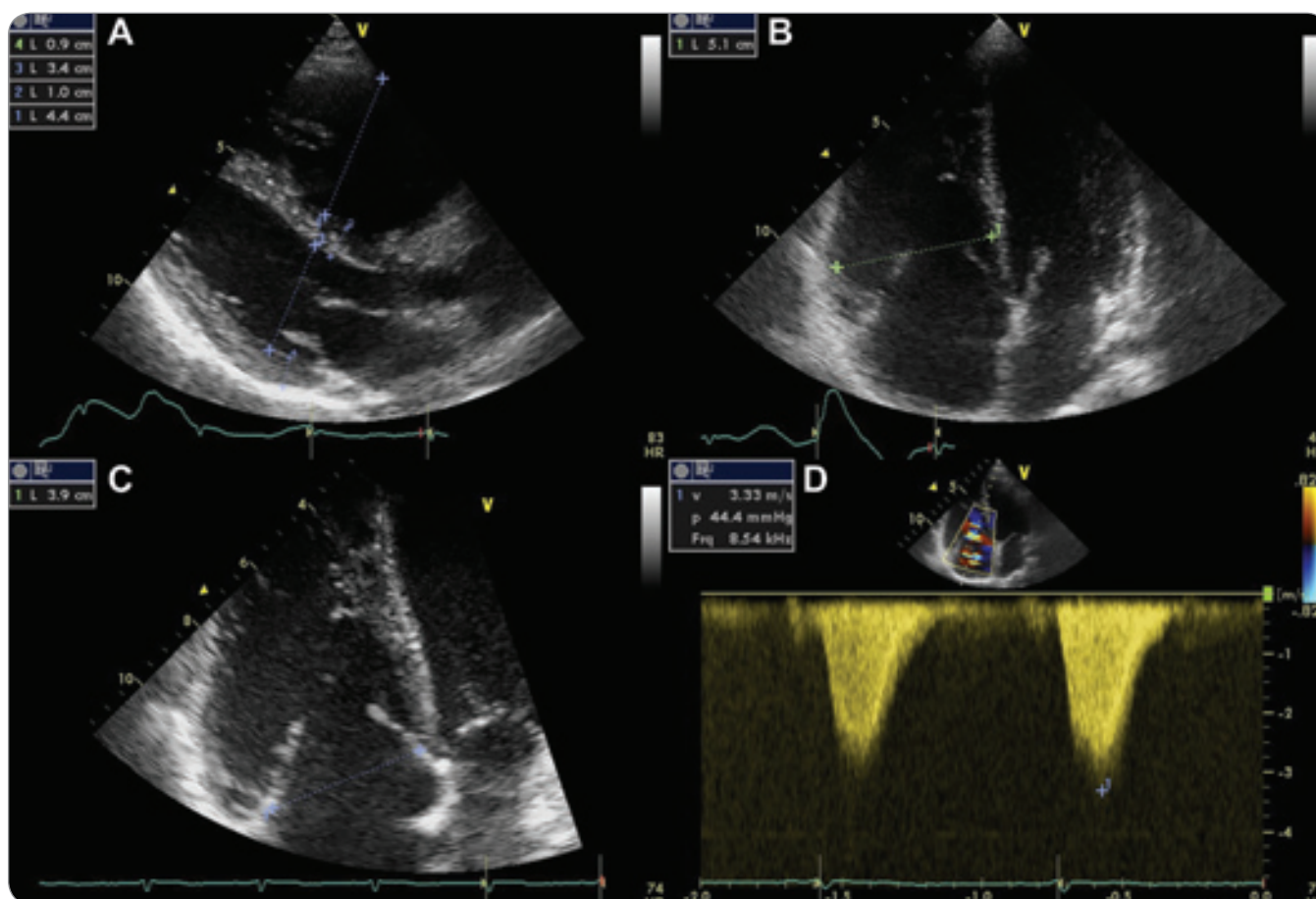


Fig. 4. Transthoracic echocardiography after six months. A) Dilated right ventricle in the parasternal long axis view; B) right ventricle and right atrium dilatation in the apical four-chamber view; C) thickened tricuspid valve leaflets, a large coaptation defect; D) continuous wave Doppler profile of severe tricuspid regurgitation. Characteristic dagger-shaped spectrum with early peak pressure and rapid decline.

paired renal perfusion and hepatic congestion. In this complex pathophysiological situation, the indication and timing of valve replacement should be determined by a multidisciplinary team.

The reported incidence of CHD has decreased as the use of SSAs has increased [6]. The present patient was treated with SSAs, which can reduce hormone secretion and inhibit tumor growth. Moreover, the patient had no symptoms or signs of heart failure, RV dilatation or dysfunction at baseline. A conservative approach was primarily decided by a multidisciplinary team consisting of a cardiologist, a cardiac surgeon, an anesthesiologist and medical oncologist. Despite SSA therapy, the CHD progressed rapidly. Chan et al. reported a series of patients with new-onset CHD in spite of SSA therapy. Clinicians should perform regular echo-

Tab. 1. Selected echocardiographic parameters.

Parameter	Baseline	Six-month follow-up
Basal RV4 diameter (mm)	40	51
RV1 diameter (mm)	31	36
ARA (cm ²)	14,2	22
RVFAC (%)	50	50
TAPSE	31	31
TA Sa	12	12
LVD D-shape	no	yes
Basal RV : LV ratio	< 1	> 1

ARA – right atrium area, LVD left ventricle diastolic, RV1 – right ventricle in the parasternal long axis view, RV4 – right ventricle in the four-chamber view, RVFAC – right ventricle fractional area change, RV : LV ratio – right ventricular to left ventricular basal diameter ratio at end-systole in the four-chamber view, TAPSE –tricuspid annular plane systolic excursion, TA Sa – peak tricuspid annulus systolic velocities derived from Doppler tissue imaging,

cardiographic screening, especially in patients with persistently increased biomarker levels (chromogranin A, or urinary 5-hydroxyindoleacetic acid), even if no cardiac involvement is present at baseline [7].

Cardiac valve replacement remains the most effective therapy for advanced CHD in patients with well-controlled systemic disease. It may relieve CHD symptoms and improve overall outcomes. Bioprosthetic valves are preferred because anticoagulation therapy is not required. The risk of bleeding is high, especially in the case of liver involvement and hepatic dysfunction. There is also a high probability of subsequent invasive procedures, which would require repeated interruption of anticoagulation therapy [8].

Progressive decline of RV function and symptoms of heart failure caused by CHD favor surgical therapy if expected survival is longer than 1 year. Emergence of severe TV regurgitation with RV dilatation and persistent symptoms or incipient deterioration of RV function is the main finding indicating the need for TV replacement. Currently, PV replacement is being performed more frequently in CHD patients, but it is unclear what degree of PV disease should warrant the intervention [5].

Recently, transcatheter valve implantation has emerged as an interesting alternative to surgical replacement in CHD. As pulmonary involvement often results in a regurgitant and stenotic PV annulus, the percutaneous approach may be considered in this situation. Loyalka et al. present a case of severe PV stenosis secondary to CHD that was successfully treated with percutaneous valve replacement [9]. Flagiello et al. re-

port a case of severe PV regurgitation secondary to CHD occurring 4 years after surgical TV replacement, successfully treated with direct transcatheter PV implantation without pre-stenting [10].

The percutaneous approach is less reproducible in tricuspid carcinoid disease, where severe stenosis is rare. Neither edge-to-edge TV repair nor orthotopic TV replacement is appropriate in the case of a large coaptation gap, severely restricted TV leaflets, and significant TV annular dilatation. Stolz et al. present a case of successful heterotopic TV replacement [11] and suggest the possibility of treating TV regurgitation by implanting two biological valves inside self-expanding stents in the superior and inferior venae cavae.

Conclusion

CHD compromise overall survival in patients with CS. The diagnosis of CS must be made as early as possible, since SSA therapy fails to induce regression of valvular lesions. Valve replacement should be considered in fully developed valvular disease; therefore, it is necessary to monitor patients regularly, including natriuretic peptide measurements and cardiac imaging. Patients remain at risk if they have high levels of vasoactive mediators despite the application of SSAs. Cardiologists and medical oncologists should be familiar with the possible manifestations of CHD.

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Authors' contributions

All authors contributed extensively to the work presented in this paper. Ivona Šimková: manuscript writing, data collection, literature search, Renata Aiglová: review and editing Filip Koubek: echocardiography images interpretation, Jan Přeček: data collection, Jan Látal: data collection, Eva Buriánková: acquired PET/CT images, images interpretation, Libuše Quinn: acquired SPECT/CT, images interpretation, Lenka Henzlová: acquired SPECT/CT images, images interpretation, Miloš Táborský: review and editing, supervision, Hana Svěbišová: follow-up of the patient, Lucie Tučková: description of histology and immunohistochemistry, images interpretation, Bohuslav Melichar: review and editing, supervision.

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