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CASE REPORT

Carcinoid heart disease involving the left heart: a case report and biomarker analysis

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Abstract

Herein, we report the case of a 67-year-old woman who was admitted to our hospital because of dyspnoea and oedema of the lower extremities. Transthoracic echocardiography revealed severe tricuspid and mitral regurgitation, and the leaflets of the tricuspid valve were found to be rigid and almost immobile. The plasma concentrations of serotonin and chromogranin A were elevated, and hence, suspicion for carcinoid heart disease was raised. In addition to the diagnostic workup and medical and surgical treatment, we analysed levels of novel cardiovascular biomarkers throughout the entire follow-up by means of enzyme-linked immunosorbent assay. A dopa positron emission tomography (DOPA-PET) was conducted and showed a neoplasm in the terminal ileum. Tricuspid valve replacement, mitral valve repair, and a closure of the patent foramen ovale (PFO) were conducted. Two months later, hemicolectomy and liver segment resection were performed. The tumour was resected, and the diagnosis of a neuroendocrine tumour (NET) was confirmed. Throughout the follow-up, we observed a decrease in the plasma levels of novel biomarkers [e.g. interleukin-8 (IL-8), soluble suppression of tumorigenicity-2 (sST2), and heart-type fatty acid-binding protein (H-FABP)] over the follow-up period. In our case, carcinoid heart disease resulted in a severe tricuspid regurgitation as commonly seen in these patients. Moreover, a pre-existent mitral regurgitation was likely aggravated by fibrotic remodelling, because a PFO has led to a right-to-left shunt and might have caused left heart involvement. As IL-8 was associated with adverse outcomes in patients with NETs, and sST2 and H-FABP were associated with adverse outcomes in patients with heart failure previously, these biomarkers could aid in the risk stratification of patients with NET.

Keywords Carcinoid syndrome; Heart failure; Tricuspid regurgitation; Mitral regurgitation

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Introduction

Neuroendocrine tumours (NETs) represent a rare class of neoplasms with an incidence between 2.5 and 5 cases per 100 000 people.[1,2] It is also a rare cause of acquired valvular heart disease, although cardiac involvement has been described in up to 60% of patients with carcinoid syndrome.[1] Without treatment, carcinoid heart disease has a poor prognosis with a 3 year survival rate as low as 31% (compared with 68% in patients without concomitant heart disease).[3] Therefore, screening for heart involvement with transthoracic echocardiography is essential in patients with a newly diagnosed carcinoid tumour.[4] NETs of the small bowel, followed by the lung, large bowel, pancreas, appendix, and ovaries, have the highest incidence of heart disease.[3]

Transthoracic echocardiography is indicated in all patients diagnosed with carcinoid syndrome, and it should be performed on a routine basis every 3–6 months depending on the clinical presentation of the patient and the severity of the disease.[4] Cardiac involvement can vary widely in patients. In fact, all heart valves may be affected, but the involvement of the tricuspid valve is most common.[5] Tricuspid leaflets show a specific involvement with thickened leaflets that have reduced mobility and are retracted. The concomitant

regurgitation can vary from mild to severe.[6–8] Right ventricular volume overload can result in these two valves becoming dysfunctional and can lead to right heart failure.[9]

As serotonin produced by the carcinoid tumour is inactivated in the lungs, right-sided carcinoid heart disease is more frequent than left-sided heart involvement (>90% of the cases).[5,10] Therefore, the presence or absence of an atrial septum defect or a patent foramen ovale (PFO) needs to be thoroughly evaluated, because in the presence of PFO, left heart valve involvement is more frequent. This seemed also to be the case in our patient who we present here,[6] even though the primary cause for mitral valve regurgitation was very likely atrial fibrillation with concomitant development of mitral annulus dilation. However, the presence of right-to-left shunting and possible negative effects on the mitral valve might have further aggravated the situation. Cardiac magnetic resonance imaging and computed tomogaphy (CT) can be helpful tools to assess damage of heart structures, as well as to evaluate cardiac metastases. Nuclear medicine imaging may be useful to detect the primary tumour; however, it may be of limited use when diagnosing carcinoid heart disease, except for depicting cardiac metastases.[11]

In addition to transthoracic echocardiography, biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP), which is a well-established marker for heart failure, has been shown to also have diagnostic and prognostic relevance in patients with carcinoid tumours.[12] However, confounders may lead to false results. Foods and medications that may elevate the levels of 5-hydroxyindoleacetic acid (5-HIAA) should be avoided, and a 24 h urine sample should be taken.[6] Another biomarker is chromogranin A, which is a glycoprotein that is released from NET cells. Its levels are also associated with cardiac involvement.[12]

The combination of NT-proBNP and chromogranin A has also been shown to determine survival probability, as patients with elevated levels of both parameters have only a survival probability of 16% compared with 81% in patients with normal levels of both parameters.[12]

Case report

Herein, we present the case of a 67-year-old female patient with symptoms of right heart failure. She was initially admitted to the hospital because of suspected tumours of the liver for further evaluation. An abdominal ultrasound was performed as the patient reported diarrhoea, abdominal pain, and a weight loss of 7 kg in the last 6 months. She also reported progressive dyspnoea, swelling of the legs, and chronic fatigue and vertigo. Peripheral cyanosis, a systolic heart murmur, an arrhythmic pulse, swelling of the lower extremities, and slight signs of ascites were observed in the clinical examination. Additionally, she reported daily fever episodes and night sweats. The patient history revealed an ischaemic stroke 14 years prior, arterial hypertension, osteoporosis, mild tricuspid regurgitation, moderate mitral valve regurgitation, and multiple hemangiomas of the liver. She was on oral anticoagulation (acenocumarol) for permanent atrial fibrillation.

Upon admission, the blood results showed hypokalaemia (potassium 3.0 mmol/L, normal value 3.6–5.0), a slight elevation of troponin (15 ng/L, normal value < 14 ng/L) and NT-proBNP (1387 pg/mL, normal value < 100 pg/mL), and a decrease of the thrombocyte count (thrombocytes 131 g/L, normal value 140–400 g/L). The other laboratory parameters did not show any abnormalities. Please see Supporting Information for ECG, chest X-ray and laboratory parameters.

Electrocardiography showed atrial fibrillation with a heart rate of 88 b.p.m., a right axis deviation, and a regular formation of the QRS complex.

Transthoracic echocardiography showed a moderately reduced left ventricular systolic function (left ventricular ejection fraction 42%), a moderate mitral regurgitation, massive right atrial dilatation (volume 202 mL), a slightly reduced right ventricular function (tricuspid annular plane systolic excursion 15 mm), and a large coaptation defect (23 mm) of the rigid and almost immobile tricuspid valve leaflets, resulting in severe tricuspid regurgitation (*Figure 1*). Systolic pulmonary artery pressure was found to be 19 mmHg, but it was probably underestimated in this setting. Transesophageal echocardiography was conducted, and severe tricuspid valve regurgitation was confirmed. Moreover, a PFO was detected.

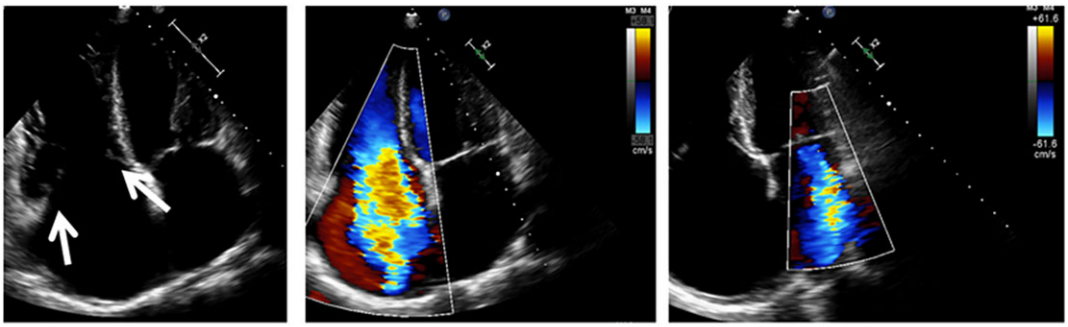
Upon coronary angiography, only a minor plaque in the proximal left circumflex artery (RCX) was found. Right heart catheterization showed only a mild elevation of the pulmonary pressure [pulmonary capillary wedge pressure mean 18 mmHg, pulmonary artery pressure systolic/diastolic/mean 33/9/21 mmHg, right ventricular mean 14 mmHg, right atrial mean 21 mmHg, cardiac output 386 L/min; pulmonary vascular resistance 148 dyn·s·cm^{-5} (1.85 Wood units), left ventricular end-diastolic pressure 12 mmHg].

Suspicion for carcinoid syndrome was raised, and consequently, plasma and urine biomarkers were measured. Urinary 5-HIAA excretion was severely elevated [87 mg/24 h (normal range 2–9 mg/24 h)]. In addition, serum serotonin [596 U/L (normal range 117–194 μg/L)] and chromogranin A [486 U/L (normal range < 34 U/L)] levels were elevated >10-fold.

A DOPA-PET showed a neoplasm in the terminal ileum, which was identified as the primary tumour. Furthermore, metastases were found in the liver (in segments VI, VII, and III) and in the mesenteric lymph nodes.

To confirm the diagnosis, an ultrasound-guided biopsy of one of the liver metastasis was performed, and the diagnosis of a NET with positive staining for CDX2, chromogranin A, and synaptophysin was proven by histology. Ki-67 index was 1%, and a somatostatin receptor scintigraphy showed a negative result.

Figure 1 Echocardiographic images. Left: echocardiographic image showing the rigid tricuspid valve. Middle: very severe tricuspid regurgitation with an enormous jet reaching the atrial roof. Right: severe mitral regurgitation with a concentric jet.



After a treatment with subcutaneous somatostatin, lanreotide, and neurohumoral therapy was started, the case was discussed in a multidisciplinary team, and an open-heart surgery was planned.

As tricuspid valve repair was not feasible owing to severe fibrosis of the valve leaflets, a valve replacement (Edwards St. Jude Epic, 33 mm bioprosthesis) was performed on the 12th of December 2015. Upon surgical inspection, the mitral valve showed only marginal sclerosis. Mitral valve reconstruction (Edwards Physio Ring, 30 mm) and a closure of the PFO were performed.

The involvement of the left heart is not commonly seen in patients suffering from carcinoid heart disease. Usually, carcinoid heart disease affects predominantly the right heart and leads to fibrosis of the tricuspid valve leaflets and consequently tricuspid valve regurgitation due to the circulation of serotonin in the blood stream and activation of pro-fibrotic signals in endothelial cells. The patient had a history of atrial fibrillation for many years, which very likely had led to a dilation of the left atrium and the mitral valve annulus and consequently also some kind of mitral regurgitation. This, however, was possibly further aggravated by a right-to-left shunt. Left heart failure, which is very rare in the carcinoid heart disease, was observed in this patient.

After discharge, the patient initially showed a good recovery, which was documented by decreasing levels of NT-proBNP over the follow-up period. Two weeks after discharge, however, the patient was readmitted to our hospital because of peripheral oedema. The patient received loop diuretics and was transferred to the Department of Surgery in February 2016. A right hemicolectomy, a cholecystectomy, and a bi-segment resection of segments VI and VII of the liver was performed 2 months later; segment III was ablated with microwave technology (2 × 100 W for 2 min). TNM staging was G1, pT1, pN1 (2/16), L0, V0, Pn0, pM1, and R0 for the primary tumour and R1 for liver metastases. Following R1 resection of the hepatic metastases, somatostatin therapy was continued. An adjuvant somatostatin therapy was planned and administered every 4 weeks post-surgery. A DOPA-PET control was performed in June 2016, and no neoplasms were found.

One year after the abdominal surgery, a control echocardiography showed adequate function of the reconstructed mitral valve as well as the replaced tricuspid valve, and the patient was in New York Heart Association Stage II. In a recent follow-up examination in September 2017, our patient presented with a liver lesion suspicious for a metastasis in the segment IVb as confirmed by follow-up PET–CT and underwent an atypical liver resection of the affected segment. In the interdisciplinary tumour board, a treatment with everolimus and lanreotide was discussed but not yet administered. The following PET–CT in February 2018 detected a new neoplastic enhancement in the infrarenal lymph nodes, and the therapy with everolimus was started. Upon echocardiography at a follow-up visit in November 2017, a slight recrudescence of the mitral valve reconstruction, corresponding to a mild, central mitral regurgitation was found. The patient is still under follow-up and is clinically stable.

Cardiovascular biomarkers

Additionally, we measured the concentrations of further biomarkers. Novel cardiovascular biomarkers, such as soluble suppression of tumorigenicity-2 (sST2), growth differentiation factor-15 (GDF-15), cardiac myosin-binding protein C (cardiac MyBP-C), interleukin-8 (IL-8), and heart-type fatty acid-binding protein (H-FABP) have been associated with inflammatory and ischaemic processes in patients suffering from chronic heart failure Moreover, recent trials have shown that these biomarkers could potentially aid in the risk stratification of patients suffering from ischaemic or dilated cardiomyopathy.[13] Recent studies showed significantly elevated biomarkers (sST2, GDF-15, and H-FABP) in patients with acute myocardial infarction or heart failure

than in patients without coronary artery disease and good systolic left ventricular function.[13–15] An association of these biomarkers and cardiac diseases was recently found, but additional clinical trials are warranted to investigate the clinical significance of these findings. In our patient, we wanted to investigate the concentrations of the biomarkers mentioned earlier, because they portray various pathophysiological pathways of the heart. Interestingly, a decrease of the plasma levels of the biomarkers (IL-8, sST2, H-FABP, and cardiac MyBP-C) was observed in our patient over the follow-up period (*Figure 2*).

The proangiogenic and inflammatory marker IL-8, for example, was highly expressed at the initial presentation and markedly decreased during the course of treatment. Of note, elevated plasma levels of IL-8 were associated with adverse outcomes in patients with NETs.[16] A similar trend was observed when we measured the plasma levels of sST2 throughout the follow-up period. sST2 gene is upregulated in case of myocardial strain and tissue fibrosis, and concentrations of circulating soluble sST2 are therefore increased. This could therefore be a possible additional prognostic and diagnostic biomarker in the diagnosis of carcinoid heart disease.

A further parameter of myocardial stress, H-FABP, is released from myocardial cells in case of ischaemia.[11] We observed a decrease in the plasma level of H-FABP, similar to IL-8 and sST2, in our patient. The novel biomarkers sST2, GDF-15, soluble urokinase-type plasminogen activator receptor (suPAR), and H-FABP showed a response in patients with chronic heart failure.[17] In patients with acute myocardial infarction, the biomarkers (sST2, GDF-15, H-FABP, and suPAR) were significantly elevated than in the control groups without coronary heart disease.[14]

Therapy

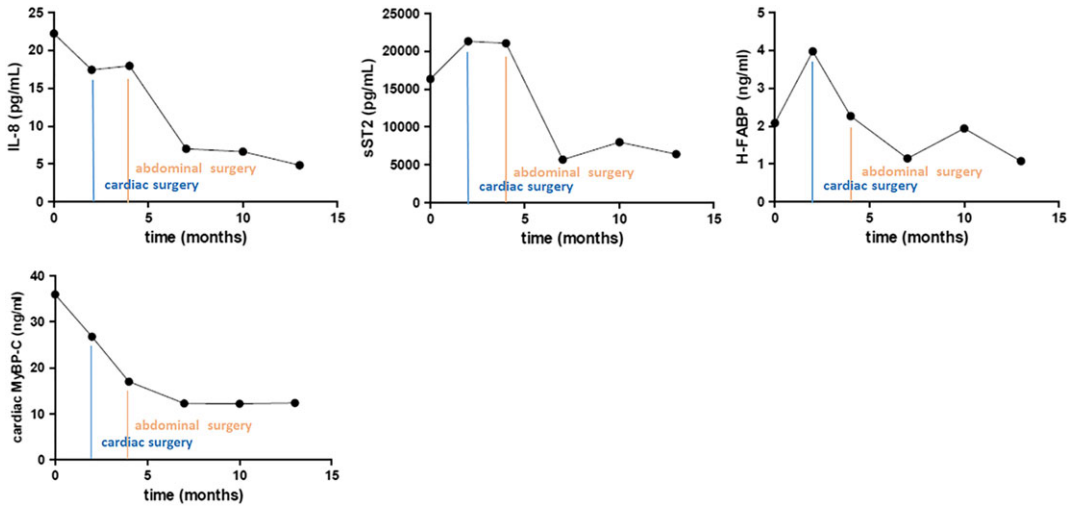
To alleviate symptoms and to prevent development of carcinoid syndrome, long-acting somatostatin analogues are used as a first-line treatment.[11] 5-HIAA levels can be reduced by telotristat etiprate, a novel serotonin synthesis inhibitor. If the disease is refractory, doses can be escalated, and interferon alpha or peptide receptor radionuclide therapy can be administered additionally.[18] Depending on the stage of the carcinoid tumour, all potentially resectable tumours (including tumours with limited metastatic disease of the liver) should be completely resected. Surgical debulking operations of large tumour areas (>90%) can result in symptom relief in 50–90% of patients.[18]

Symptomatic patients with limited disease and patients with unresectable, symptomatic disease should additionally be treated with a somatostatin analogue, which was shown to effectively control symptoms and may also control tumour growth.[18] Long-acting somatostatin analogues, for example, octreotide, bind to somatostatin receptors on the tumour cells and, therefore, inhibit release of bioactive amines. This therapy reduces flushing (81%) and diarrhoea (79%) in patients.[18]

In perioperative patients, continuous somatostatin analogue (octreotide) infusions (50–100 μg/h or more) are of great importance. These should be started 2 h prior the procedure and administered for up to 48 h post-surgery.[11] Octreotide reduces the serotonin release, optimizing the outcome with fewer perioperative complications such as hypotension, bronchospasm, flushing, carcinoid crisis, and death.[11,19]

Other modalities such as hepatic artery embolization, chemoembolization, or radioembolization are alternative

Figure 2 Cardiac biomarkers. The cardiac biomarker levels (IL-8, sST2, H-FABP, and cardiac MyBP-C) in our patient 12 months after surgery show a significant reduction. cardiac MyBP-C, cardiac myosin-binding protein C; H-FABP, heart-type fatty acid-binding protein; IL-8, interleukin-8; sST2, soluble suppression of tumorigenicity-2.



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methods as palliative therapy for symptom control.[18] Patients with carcinoid heart disease usually die because of severe tricuspid regurgitation rather than carcinomatosis.[11] In patients with carcinoid heart disease, valve surgery is the only effective therapy. Right-sided valve replacement should also be considered for patients with mild symptoms, because waiting for a progression of the symptoms can result in an increased perioperative mortality.[20] Diuretics together with fluid and salt restriction are only temporarily effective for symptom control. In advanced right ventricular failure, these therapies become ineffective.[11] Early cardiac surgery should be considered in patients before advanced heart failure occurs. This may improve the outcome of these patients.[11]

Discussion

Carcinoid heart disease is a rare cause of acquired valvular heart disease; however, if patients present with symptoms of heart failure, flushing, and diarrhoea, this differential diagnosis should be considered to initiate adequate therapy early in the course of the disease. In our case, the presentation of carcinoid heart syndrome was likely not just limited to tricuspid valve regurgitation. Upon transthoracic echocardiography, a concomitant severe mitral regurgitation was found, which was possibly aggravated by involvement of the left heart. Upon transesophageal echocardiography, we found a PFO that resulted in a right-to-left shunt, and hence, serotonin, which is usually metabolized in the lungs, could reach the left heart and aggravate (together with pre-existing atrial fibrillation) mitral regurgitation.

Supplementary methods

Measurement of clinical laboratory parameters was conducted at the Department of Laboratory Medicine (University Hospital Salzburg, Universitätsinstitut für Medizinisch-Chemische Labordiagnostik). Serum levels of IL-8, sST2, H-FABP, and cardiac MyBP-C were determined by using commercially available enzyme-linked immunosorbent assay (ELISA) kits (DuoSet ELISA, R&D Systems, USA). Preparation of reagents and measurements were performed according to the manufacturer's instructions. In short, serum samples and standard proteins were added to a multiwell plate (Nunc MaxiSorp plates, VWR International, Austria) coated with the respective capture antibody and incubated for 2 h. Subsequently, plates were washed using washing buffer (Tween 20, Sigma Aldrich, USA; and phosphate-buffered saline solution). After washing, a biotin-labelled antibody was added to each well. In the next step, wells were incubated for another 2 h. ELISA plates were washed once more, and a streptavidin–horseradish peroxidase solution was added. After the addition of tetramethylbenzidine (Sigma Aldrich, USA), a colour reaction was achieved. Optical density was measured at 450 nm on an ELISA plate reader (iMark Microplate Absorbance Reader, Bio-Rad Laboratories, Austria). GraphPad Prism software (GraphPad Software, La Jolla, CA, USA) was used for visualization of biomarker levels and time courses.

Conflict of interest

The authors declare no conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1a. ECG of the patient.
Figure S1b. X-ray of the thorax.
Table S1. Laboratory parameters of the patient at admission.

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