DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN CARCINOID HEART DISEASE. CLINICAL CASE REPORT

Rakowiakowa choroba serca – trudności diagnostyczne i terapeutyczne. Prezentacja przypadku klinicznego

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Abstract

Neuroendocrine neoplasms develop from diffuse neuroendocrine system cells and occur rare. They characterized by insidious progress and often are recognized accidentally. We present a case of a patient, who had a nephrectomy of the left kidney, due to a papillary carcinoma. While the operation, there had been discovered a focal change of mesenterium, which was taken a biopsy from. On histopathological examination, neuroendocrine neoplasm has been confirmed. The patient was treated with a long-acting somatostatin analogue. During a further observation, progression of the disease has been observed and cardiac metastasis of the neuroendocrine neoplasm was discovered, what is uncommon. Due to progression, peptide receptor radionuclide therapy was added to chronic treatment with the long-acting somatostatin analogue. Stabilization of the disease have been achieved. After 1,5 year the second progression has been observed and the peptide receptor radionuclide therapy was used one more time, which was successful. We also describe a diagnostic difficulty, caused by poor sensitivity of the most often used imaging methods of the heart, like echocardiography and magnetic resonance imaging, which are not as effective as a molecular imaging methods to recognize metastases of neuroendocrine neoplasms. Knowledge about cardiac metastases of neuroendocrine neoplasms still is little. Their impact on a course of disease and prognosis still is not known. For this reason, more investigations are needed.

Streszczenie

Nowotwory neuroendokrynne rozwijają się z komórek rozproszonego układu wydzielania wewnętrznego. Występują rzadko. Charakteryzują się podstępnym przebiegiem i często rozpoznawane są przypadkowo. Prezentujemy przypadek kliniczny pacjenta, który przebył nefrektomię lewostronną z powodu raka brodawkowatego nerki. Podczas operacji wykryto zmianę ogniskową w krezce, z której pobrano wycinki do badania histopatologicznego. Rozpoznano nowotwór neuroendokrynny. Zastosowano leczenie długodziałającym analogiem somatostatyny. W dalszej obserwacji podczas progresji choroby wykryto przerzut nowotworu neuroendokrynnego do mięśnia sercowego, co zdarza się niezwykle rzadko. W związku z progresją do przewlekłego leczenia długodziałającym analogiem somatostatyny dołączono radioizotopową terapię celowaną molekularnie. Uzyskano stabilizację choroby. Po upływie 1,5 roku zaobserwowano drugą progresję choroby i zastosowano kolejny raz radioizotopową terapię celowaną molekularnie, z dobrym skutkiem. W pracy opisujemy również trudności diagnostyczne spowodowane zbyt małą czułością najczęściej stosowanych metod obrazowania serca, takich jak echokardiografia czy rezonans magnetyczny, które ustępują metodom obrazowania molekularnego w zakresie wykrywania przerzutów nowotworów neuroendokrynnych. Wiedza na temat przerzutów nowotworów neuroendokrynnych do serca jest nadal niewielka. Nadal nie jest jasny ich wpływ na dalszy przebieg choroby i rokowanie pacjenta. W związku z tym niezbędne jest przeprowadzenie większej liczby badań.

Keywords: neuroendocrine neoplasms; cardiac metastasis; long-acting somatostatin analogue; peptide receptor radionuclide therapy

Słowa kluczowe: nowotwory neuroendokrynne; przerzuty do serca; długodziałający analog somatostatyny; radioizotopowa terapia celowana molekularnie

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Case report

A 68-year-old patient has been under the care of the Department of Endocrinology for more than a decade. At the age of 58 years, the patient, having a history of chronic abdominal pain, weight loss, left lumbar pain, hypertension, nicotinism, chronic obstructive pulmonary disease and gallbladder stones, underwent left nephrectomy due to a tumour of the left kidney (measuring 33 × 45 mm, with central lysis and with enlarged periaortic lymph nodes, detected on abdominal CT scan). During nephrectomy, the tumour (60 mm in diameter) compressing the perirenal and perihilar adipose tissue, was resected. There were no signs of invasion. Intraoperatively, a focal lesion in the mesentery was also detected and sampled. Pathological mesenteric, external iliac, periaortic lymph nodes and metastatic lesions in the liver were detected. Histopathology confirmed a pT1b papillary carcinoma of the left kidney, Fuhrman grade II, G2, while the specimen from the focal a lesion was diagnosed as a neuroendocrine neoplasm (NEN G2, Ki 67 5–7%, with positive staining for chromogranin and synaptophysin) (fig. 1).

Two months later, a positron emission tomography/computed tomography (PET/CT) scan with fluorodeoxyglucose confirmed a metabolically active lesion in the small bowel with mesenteric and abdominal lymph node involvement. ^{68}Ga-gastrin analogue PET/CT (^{68}Ga-PET/CT) detected metastatic lesions in the liver, right renal pole area, mesentery and mesenteric lymph nodes, small bowel, and the skeleton (fig. 2).

Treatment with lanreotide, a long-acting somatostatin analogue, was initiated. The patient was put under surveillance, with monitoring of chromogranin A levels and single photon emission computed tomography (SPECT) findings. Stabilisation of the disease was achieved.

^{68}Ga-PET/CT, somatostatin receptor scintigraphy/single-photon emission computed tomography/computed tomography (SRS/SPECT/CT) and CT scans performed in subsequent years did not indicate disease progression (fig. 3).

Treatment with cold somatostatin analogue was continued. Progression was observed five years after the diagnosis of NEN. An increase in chromogranin A from 287.4 ng/mL to 590.1 ng/mL was observed. SPECT/CT somatostatin receptor imaging revealed a new focus in the left part of the heart, at the base of the left ventricle, several pericardial foci, orbital foci and progression of liver and mesenteric lesions (fig. 4 and fig. 5).

Echocardiography raised the suspicion of carcinoid heart disease. Magnetic resonance imaging (MRI) of the heart was ordered due to obesity and difficult examination conditions. It showed an undilated left ventricular cavity, with normal systolic function and an ejection fraction (EF) of 60%, segmental thickening of the septal, anterior and lateral wall up to 22 mm, and impaired blood flow in the thickened anterior/posterolateral wall muscle. The right ventricular cavity was also undilated, with a normal global EF of 57%. Thickening of right ventricular muscle, tricuspid valve leaflets and chordae tendineae (features

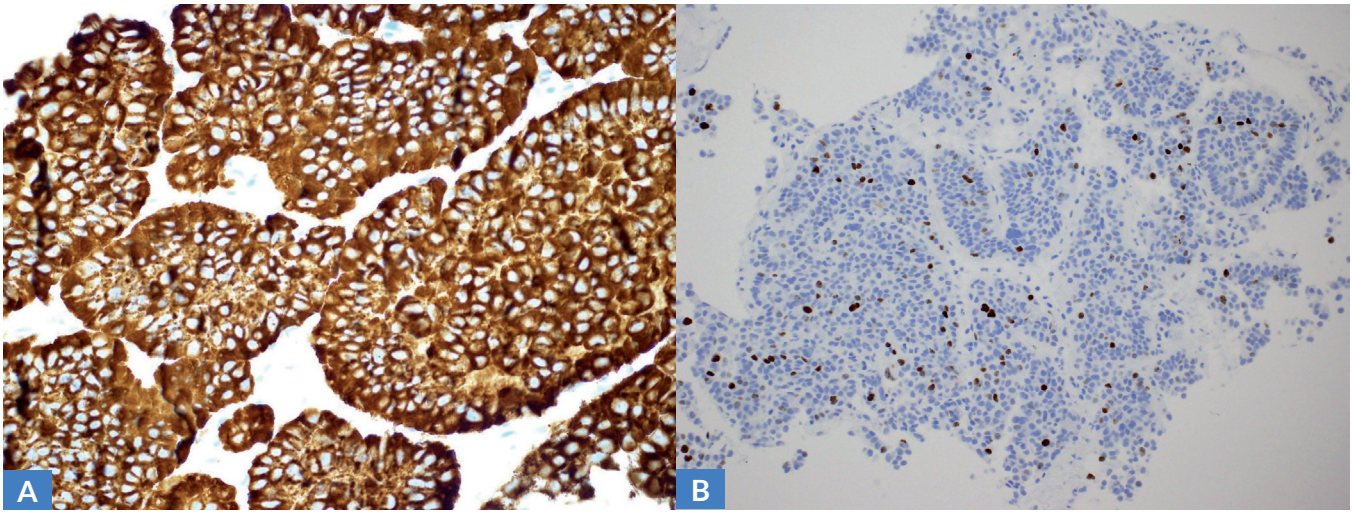

Figure 1. Microscopic image of a section taken from a focal mesenteric lesion. **A.** Positive immunohistochemical reaction with chromogranin (magnification 400 ×). **B.** Approximately 5–7% of tumour cell nuclei were stained in the reaction with anti-Ki67 antibody (clone MIB-1) (200 ×).

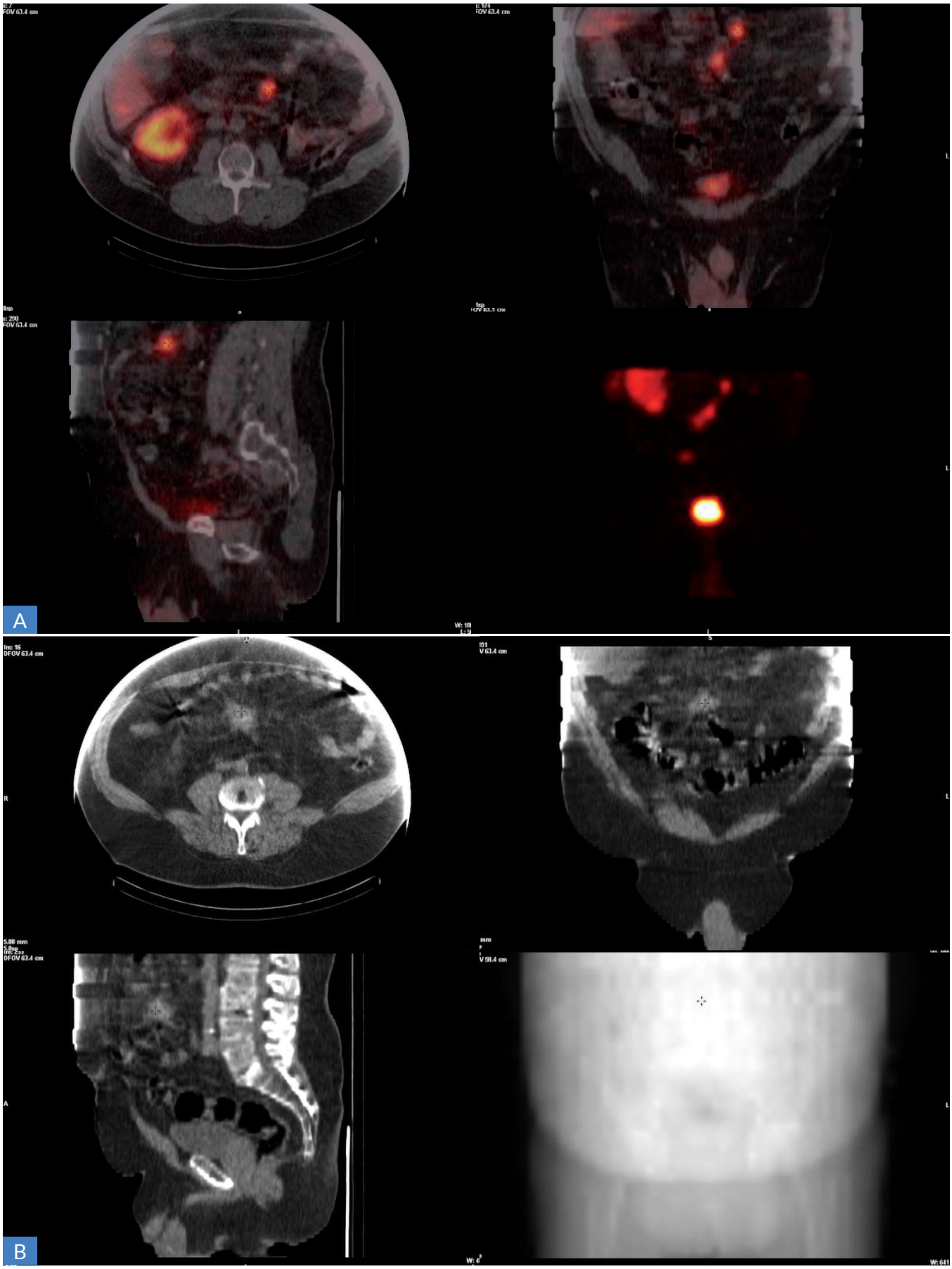

Figure 2. A. ^{68}Ga-PET/CT. A focal lesion in the mesentery with overexpression of type 2 somatostatin receptors was confirmed. Metastatic lesions were found in the liver, the lower pole area of the right kidney, the mesentery, mesenteric lymph nodes, small bowel and skeletal system. **B.** Abdominal CT. A star-shaped focal lesion causing a desmoplastic reaction with calcifications was found in the mesentery.

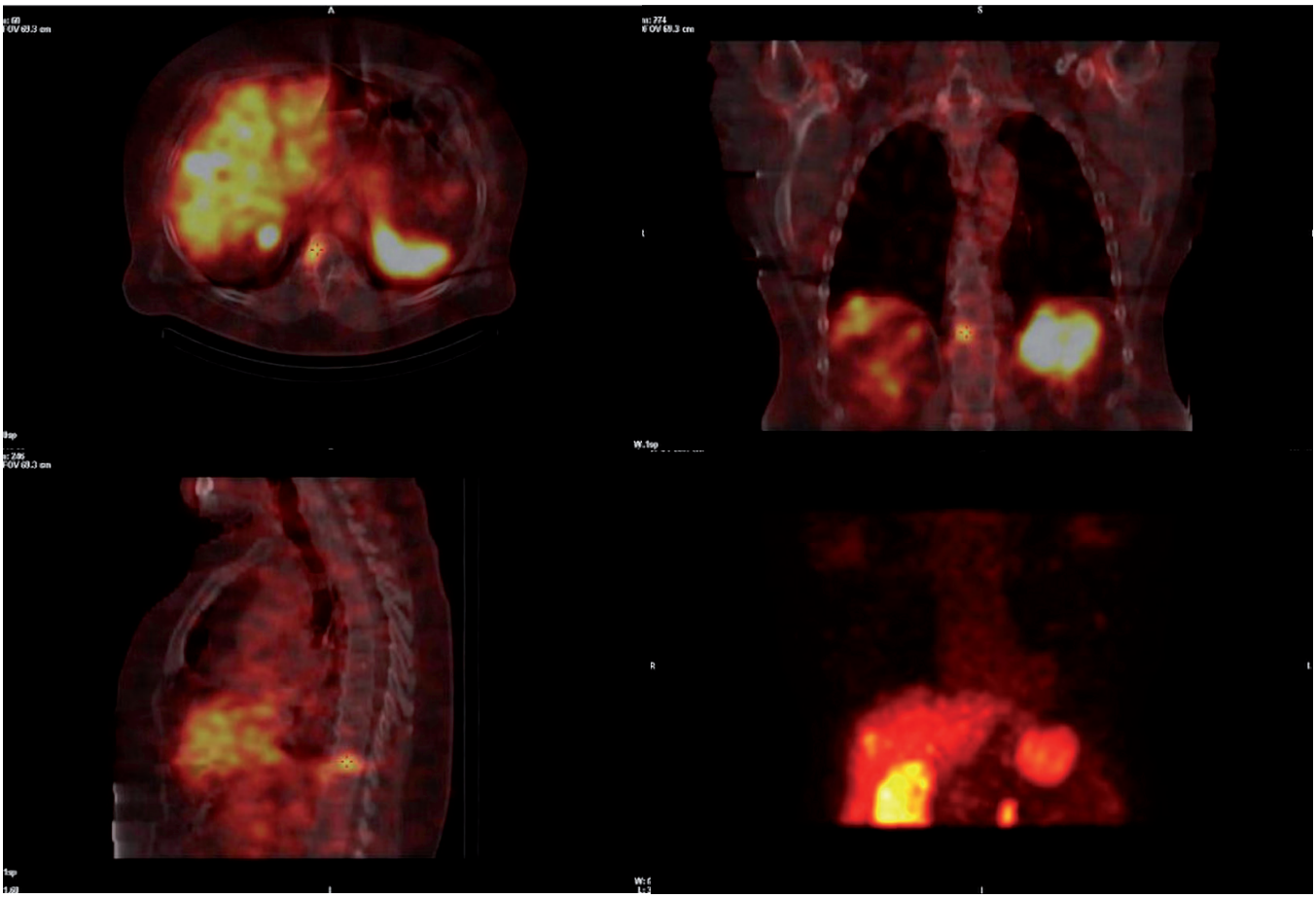

Figure 3. SPECT/CT. Stabilisation of the disease. Pathological overexpression in the liver, mesenteric ileum, at the upper pole of the Th12 vertebra and at the upper pole of the right kidney

of restriction) was observed. There were no myocardial or pericardial focal lesions that would differ in signal on T1-weighted images before and after contrast agent administration. There were no signs of metastatic lesions in the myocardium or pericardium. Late enhancement images after contrast administration showed features of diffuse intramuscular fibrosis in the left and right ventricular muscle; the most severe lesions were located in the thickened muscle in the basal segments of the anterior and anterolateral wall, and in the interventricular septum at the superior and inferior junctions of the right and left ventricles.

Carcinoid heart disease was diagnosed. In view of disease progression, treatment with hot somatostatin analogues ^{177}Lu-DOTA-TADE was administered and long-acting somatostatin analogue was continued. The patient underwent four cycles of peptide receptor radionuclide therapy (PRRT). A total of four 200 mCi cycles of ^{177}Lu-DOTA-TADE were administered and disease stabilisation was achieved. At follow-up 1.5 years after the last administration of PRRT, a ^{68}Ga-PET/CT scan was performed, diagnosing overexpression of somatostatin receptors in the mediastinal lymph nodes and right orbit, multiple foci in the skeleton, infiltrative lesions in the mesentery of the intestine, and two foci in the myocardium (fig. 6).

A 24-h urine collection showed increased 5-hydroxyindoleacetic acid (5-HIAA) excretion (63.1 mg/day [normal 0.5–9 mg/day]) and excluded increased metoxycatecholamines excretion. Echocardiography showed no organic changes or haemodynamically significant valvular defects, no features of cardiac carcinoid disease and failed to visualise the described intracardiac metastatic lesions. Chromogranin A increased from 687.6 ng/mL to 1704.0 ng/mL over a period of 7 months. Further disease progression was observed. The patient was not qualified for mTOR inhibitor treatment due to lack of reimbursement for the treatment and the location of the primary lesion, and was qualified for repeat PRRT instead. The patient received further four cycles of treatment, achieving disease stabilisation (fig. 7).

Discussion

The case presented here demonstrates the importance of adequate therapy and an individualised approach to a NEN patient.

Metastatic cardiac tumours (MCTs) are rare, detected in 1.5–20% of autopsies of cancer patients. They are usually clinically silent. Although any cancer can lead to distant cardiac metastases, melanoma, lymphomas, leukaemias, lung, breast and oesophageal cancers are most likely, whereas intracardiac NEN metastases are very rare [5].

In the case of NEN, cardiac metastatic lesions are extremely rare due to the frequency of these tumours. The liver and lymph nodes, followed by the skeleton, lung and peritoneum, are the most common NEN metastasis sites [5]. In recent years, less common metastatic sites

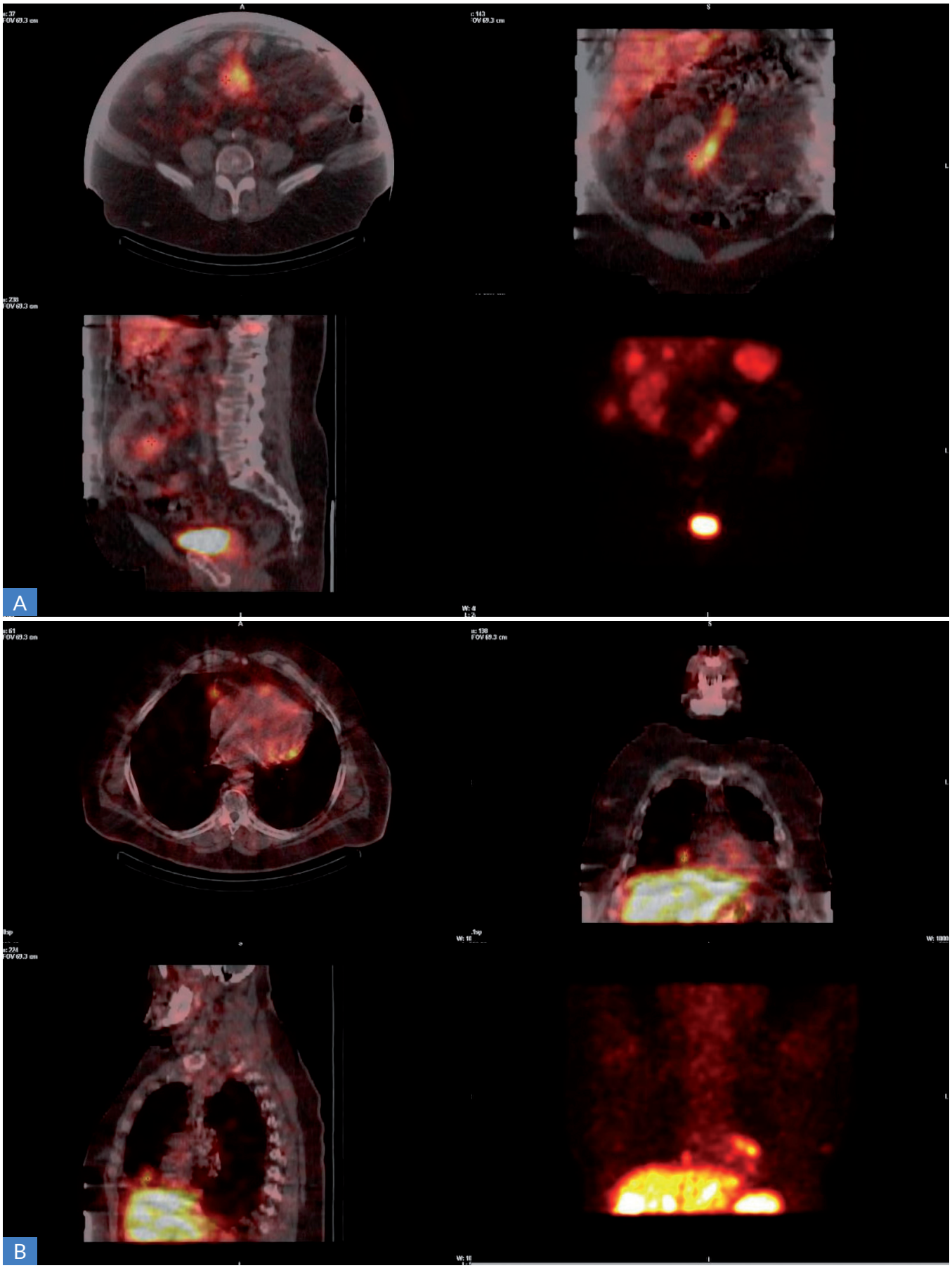

Figure 4. SPECT/CT. Progression of the disease. **A.** Pathological overexpression in the liver, intestinal mesentery, at the upper pole of the right kidney and in the Th12 vertebral body. **B.** Additional focal lesions in the heart, orbits, subcutaneous tissue of the chest (in the right breast view); progression of liver lesions

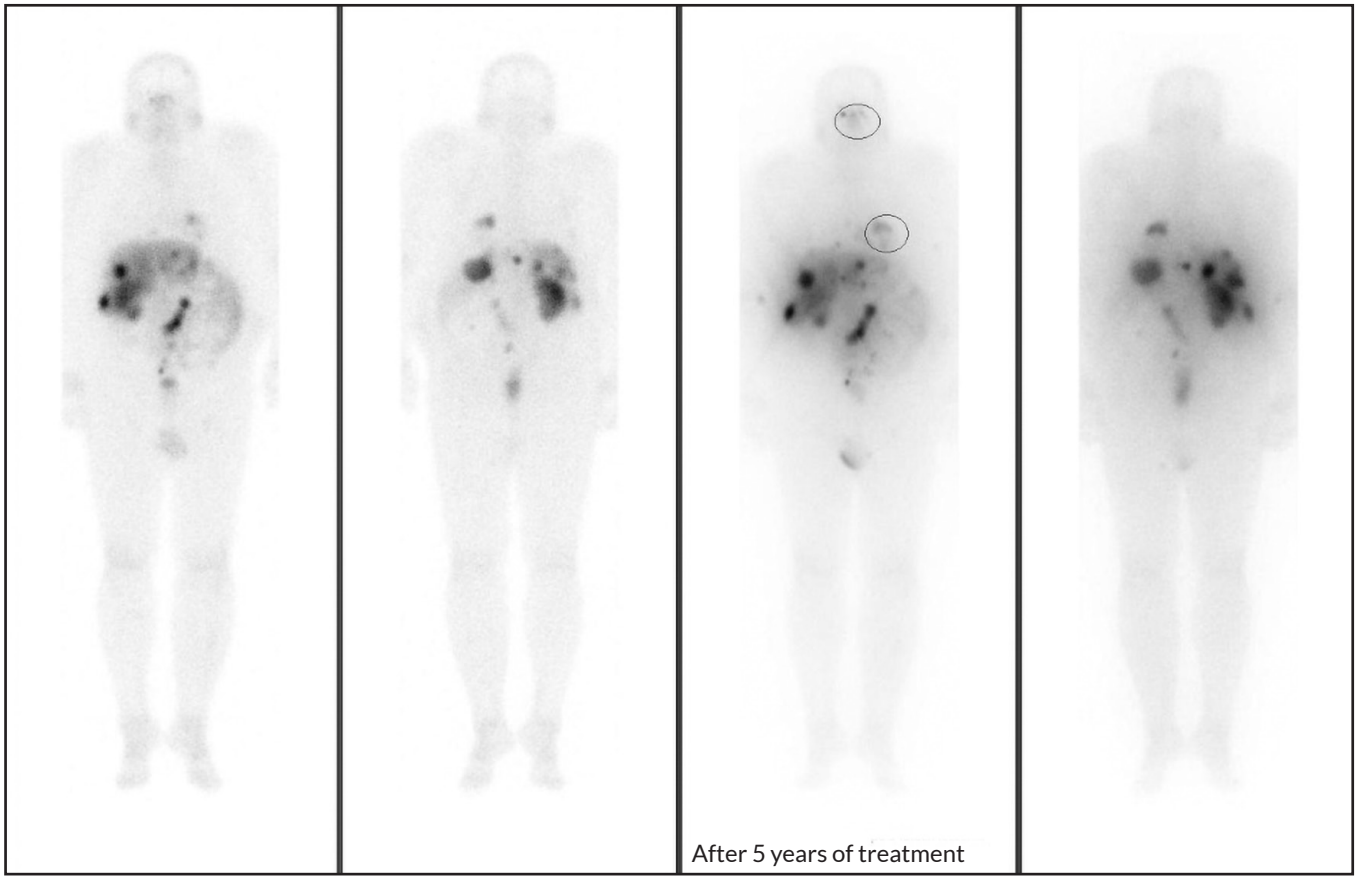

Figure 5. Somatostatin receptor scintigraphy (SRS). Evident progression of lesions after 5 years of treatment with a long-acting somatostatin analogue. Additional focal lesions in the heart, orbits, subcutaneous tissue of the chest (in the right breast view); progression of liver and mesenteric lesions

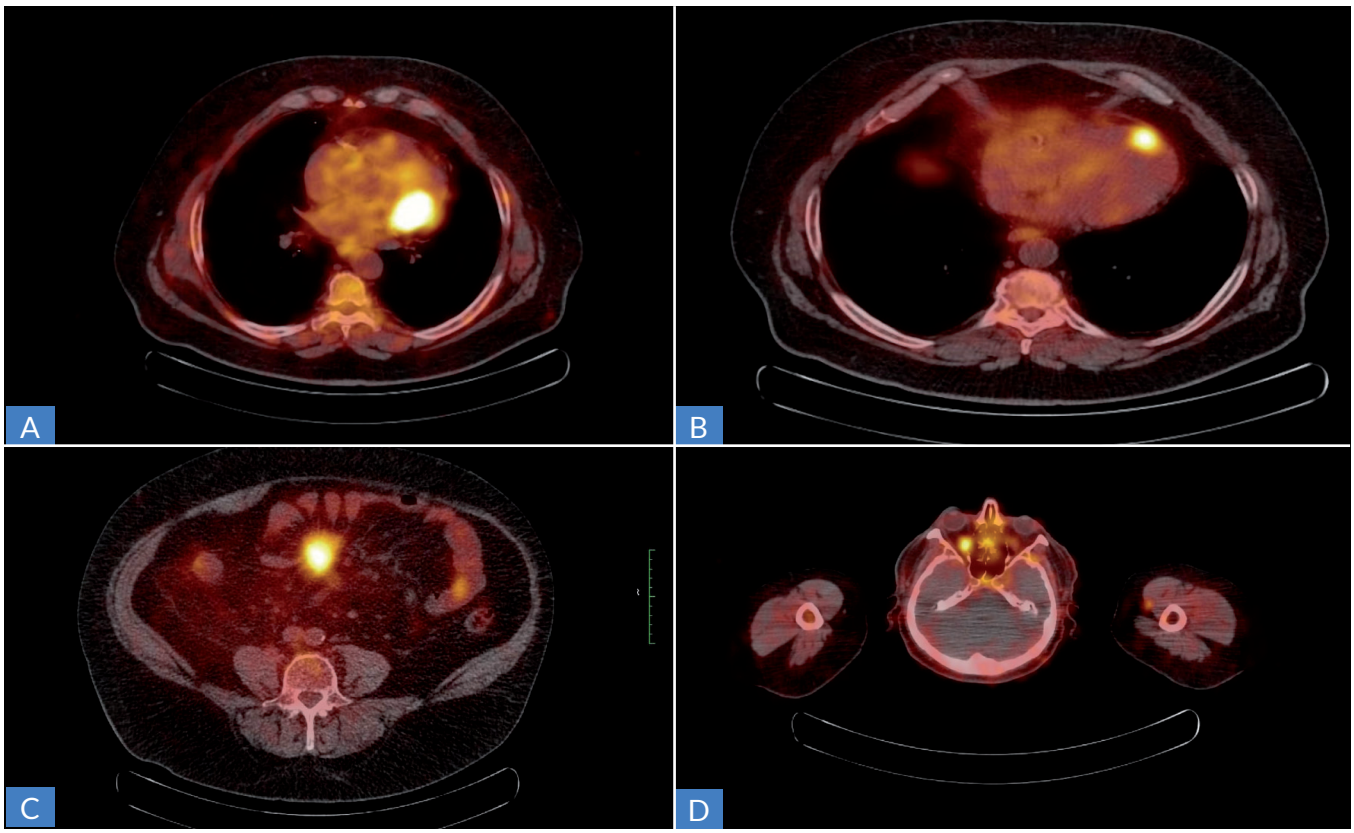

Figure 6. ^{68}Ga-PET/CT. Overexpression of somatostatin receptors. **A, B.** Two focal lesions in the myocardium. **C.** A focal lesion in the mesentery of the small intestine. **D.** A focal lesion in the right orbit

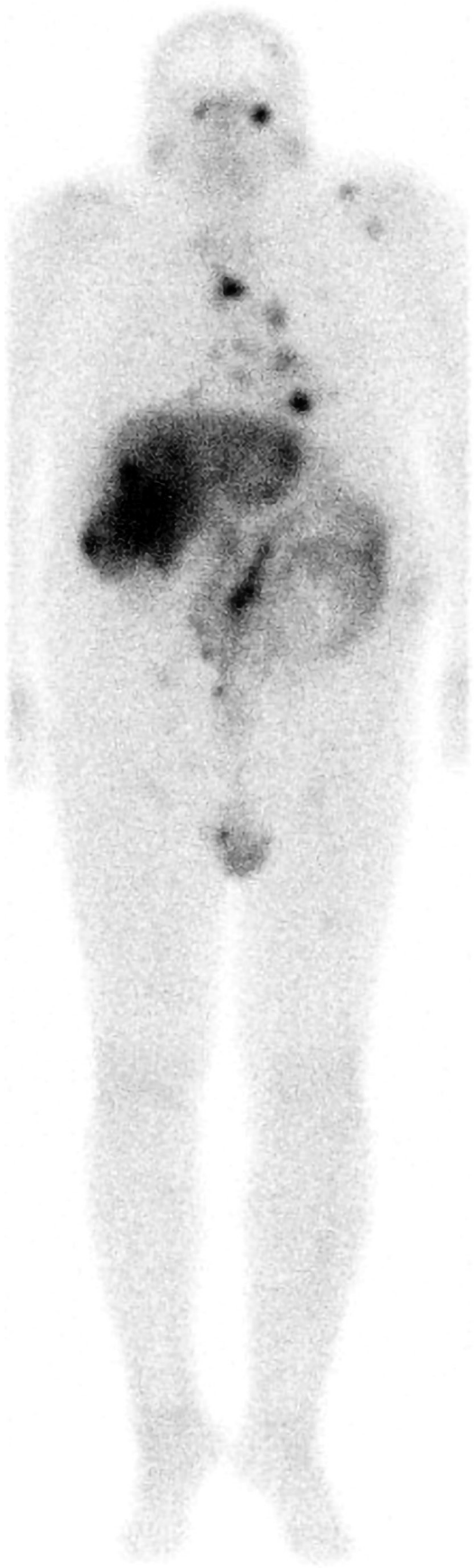

Figure 7. Follow-up scintigraphy after the second treatment cycle with hot somatostatin analogues. Stable lesions. No new foci of increased pathological radiotracer accumulation

such as the brain, breast, ovaries, adrenal glands, skin or heart have been increasingly reported due to advances in molecular imaging. Echocardiographic detection of cardiac metastatic lesions is difficult, mainly because lesions smaller than 10 mm are not visible. Although cardiac MRI is the imaging modality of choice in the assessment of tumours and myocardial invasion, the case described here shows that it has lower sensitivity compared to molecular imaging methods. Somatostatin receptor scintigraphy has a high sensitivity and allows imaging of metastatic lesions that are not visible with other methods. ^{68}Ga-PET/CT remains the tool with the highest sensitivity in NEN imaging.

To date, only one meta-analysis has been conducted on the incidence and location of intracardiac metastases arising from NEN, as well as their impact on ejection fraction and survival rates. In this study, conducted by Hamza et al., cardiac metastatic lesions were found in 2.3% of patients (257 cases) out of the 16,685 NEN cases analysed. These lesions were most often detected by ^{68}Ga-PET/CT. The left ventricle (48%), followed by the pericardium, right ventricle, interventricular septum, left atrium, and right atrium, was the most common site of intracardiac NEN metastases. Reduced EF, occurring in 15% of patients, was the most common clinical manifestation of intracardiac NEN metastases. However, the majority of patients did not have reduced EF excluded before the diagnosis of cardiac metastases. The mean survival of patients from the time of intracardiac NEN metastasis diagnosis was 35.89 months. In the case presented here, the patient has lived for more than seven years since the diagnosis of metastatic lesions. He does not present with cardiac arrhythmias or symptoms of heart failure.

Conclusions

Intracardiac NEN metastases are very rare and usually asymptomatic. Their detection may require the use of imaging modalities with the highest sensitivity, such as ^{68}Ga-PET/CT. There are no precise data on their possible impact on myocardial complications, such as arrhythmias, conduction blocks, heart failure, valvular defects or acute coronary syndromes. Further studies are needed to determine the definitive impact of cardiac metastases on the survival of NEN patients.

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