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An atypical course of pancreatic neuroendocrine tumour manifesting as cardiac metastasis — a clinical case

Nietypowy przypadek przebiegu nowotworu neuroendokrynnego trzustki pod postacią przerzutu do serca — opis przypadku klinicznego

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Abstract

This paper presents a ten-year course of the disease in a patient with pancreatic neuroendocrine tumour NEN G1, and with confirmed single, asymptomatic metastasis to the left cardiac ventricle. Initially, the cardiac metastasis was visible only on a positron emission tomography (PET) scan using gallium-68-labelled somatostatin analogue; the sensitivity of an echocardiography scan was lower. Despite the advanced stage of the disease, surgical excision of the cardiac metastasis was performed. The patient underwent a total of eight operations, and received chemotherapy, radiotherapy and somatostatin analogues. Currently, he is on a targeted therapy with everolimus. As a result of the treatment, the patient remains in a good general condition. This is the second described case of cardiac metastasis of PNEN. Using different methods of treatment in the case of generalised pancreatic neuroendocrine tumour with low proliferative potential, patients are offered the chance to prolong their survival and maintain a good quality of life. **(Endokrynol Pol 2014; 65 (3): 232–237)**

Key words: *pancreatic neuroendocrine neoplasm; somatostatin analogue; cardiac metastasis*

Streszczenie

W pracy przedstawiono 10-letni przebieg choroby u pacjenta z nowotworem neuroendokrynnym trzustki NEN G1, u którego stwierdzono pojedynczy, bezobjawowy przerzut do lewej komory serca. Przerzut do serca widoczny był początkowo jedynie w badaniu pozytronowej tomografii emisyjnej z użyciem analogu somatostatyny znakowanej galem-68 , czułość badania echokardiograficznego była mniejsza. Pomimo zaawansowanej choroby wykonano operacyjne usunięcie przerzutu z serca. W sumie chory był 8-krotnie operowany, otrzymywał chemioterapię, radioterapię oraz analogii somatostatyny, a obecnie prowadzona jest terapia celowana everolimusem. W wyniku zastosowanego leczenia chory pozostaje w dobrym stanie ogólnym. Jest to drugi opisany przypadek z przerzutem PNEN do serca. Stosowanie różnych metod leczenia w przypadku uogólnionego nowotworu neuroendokrynnego trzustki o niskim potencjale proliferacyjnym daje szansę na wydłużenie przeżycia przy zachowaniu dobrej jakości życia. **(Endokrynol Pol 2014; 65 (3): 232–237)**

Słowa kluczowe: *nowotwór neuroendokrynny trzustki; analog somatostatyny; przerzut do serca*

Introduction

The frequency of diagnosing neuroendocrine neoplasms of the gastrointestinal system has been on the rise due to both an actual increase in the incidence of the disease and advances in the diagnostics of these tumours. According to various sources, pancreatic neuroendocrine tumours (PNENs) constitute from 2% to 10% of all tumours affecting this organ [1–3]. The incidence of PNENs is estimated to be 0.32/100,000/year [4]. PNENs are classified as being either functioning and non-functioning. The former constitute 10–30% of cases and are associated with symptoms of hormone excess. The latter constitute approximately 50–80% of cases and do not produce sufficient amounts of hormones and/or biogenic amines to produce clinical symptoms [5]. The implementation of the new WHO classification in 2010 modified the terminology of neuroendocrine tumours. The term "neuroendocrine tumours/neoplasm" (NET/NEN) refers to highly differentiated tumours, such as NEN G1 (Ki-67< or = 2%) and NEN G2 (Ki-67 3–20%). Moreover, one can distinguish neuroendocrine carcinoma NEC from mixed adenoneuroendocrine carcinoma MANEC [6, 7]. Radical surgical treatment is the only fully effective curative procedure [8]. The majority of patients are diagnosed at an unresectable or metastatic stage of the disease. Patients with low or intermediate

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grade advanced disease have a median survival time of 24 months, while patients with poorly differentiated tumours have a median survival time of approximately ten months [9, 10].

In cases of advanced PNENs, various treatment methods are used, including cytoreductive surgeries, biotherapy with labelled somatostatin analogues, isotope radiation therapy, chemotherapy and targeted medication [4, 8, 11–13]. Pancreatic neuroendocrine neoplasms primarily metastasise to the liver, lymph nodes and bones [5]. Metastases to mediastinal structures are infrequent. Cardiac metastases in PNENs are case-based reasoning. To date, one case has been published concerning a patient diagnosed with PNEN G2, with multiple synchronous metastases to the lymph nodes, bones and the heart found upon diagnosis [14].

This report describes the course of a ten-year treatment of a patient with pancreatic NEN G1, diagnosed with metastasis to the left ventricle of the heart, who underwent successful operation. The ongoing follow-up systemic treatment makes it possible to prolong the patient's survival period.

Case report

A 40-year-old man had been experiencing slight pain in the right epigastric region and dyspepsia for two years. An abdominal ultrasound revealed a tumour of 30 mm in diameter in the head of the pancreas, and an abdominal CT scan showed abnormal image of the pancreas. The patient reported to the Oncology Centre in Gdańsk, where he stayed until October 2011.

In September 2003, an operation was performed (*Operatio modo Whiple with excisio partialis vena cava inferior*). Histopathological examination revealed *Carcinoma neuroendocrinale* G3 (WHO 2000), ceratine (+), focus chromogranin (+), synaptophizin (+), S-100 (+), peripancreatic lymph nodes with metastases, malignant infiltration of the lymph nodes exceeds bags and covers the surrounding adipose tissue. After two years, a tumour was confirmed in the abdominal wall. In March 2004, the patient was operated on (*excisio tumour tegmentis abdominis*). Histopathological examination showed no tumour cells. In September 2005, a positron emission tomography scan with fluorine-labelled glucose analogue (18FDG-PET/CT) was performed, revealing foci of an active malignancy process in the abdominal cavity in the form of changes in the aortic area (diameter: 19 and 16 mm, Standardized Uptake Value — SUV 18.1), a change close to the cavity of the right kidney (diameter: 30 mm — SUV 22.8), a change on the left side of the aorta (diameter: 19 mm — SUV 16.4), a change around the right iliac vessels (diameter: 17 mm — SUV 21.5), and a change at the L3 area on the left side of the aorta (diameter: 11 mm — SUV 8.8). In October 2005, an exploratory laparotomy was performed and specimens were collected for histopathological consultation, which revealed *Carcinoma neuroendocrinale metastaticum*. A positron emission tomography scan using gallium-68-labelled somatostatin analogues (^{68}Ga-PET/CT) revealed lack of somatostatin receptor expression, disseminated disease and no hormonal activity of the tumour. Further CT scans and ^{18}FDG-PET/CT confirmed progression of the disease. The patient was qualified for chemotherapy and received six courses of streptozotocin plus 5-Fu from March to August 2006. Due to a new focus in the right ureter area with pressure on the ureter, the patient was re-operated on in 2006 — partial resection of the right ureter. A decision was then made to start somatostatin analogue therapy, which was continued until June 2007. In October 2008, a metastatic tumour was removed from the retroperitoneal space. From January to March 2009, the patient received radiation therapy at the site of the removed mid-abdomen recurrence (the total dose of 54 Gy, in 30 fractions). Further ^{18}FDG-PET/CT revealed recurrence in the retroperitoneal space; another surgery to remove the recurrence was performed in October. In January 2010, a ^{18}FDG-PET/CT scan revealed new foci of the disease: a change in the left ventricle (13 × 15 mm — SUV 11.3), a change in the liver (13x15 mm), a change in the aortic region (10 × 15 mm — SUV 8.6). The^{18}FDG-PET/CT scan was repeated in November 2010, revealing metabolic progression of the disease and the ^{68}Ga-PET/CT scan showed that somatostatin receptors were present in the foci. Chromogarnin A was elevated at 588 ng mL (norm < 100). Echocardiography, which was performed twice, did not confirm any pathology; in particular, the left ventricle showed no hypertrophy or sections of disturbed contractility, and had proper ejection fraction. The patient had problems with both flatulence and diarrhoea, but no weight loss occurred. A somatostatin analogue therapy was started. The ^{68}Ga-PET/CT scan was repeated in April 2011, revealing progression of the disease (a change around the intestinal loop — 16 mm, SUV 43.5 (Fig. 1); changes in the aortic region — 24 × 17 × 29 mm, SUV 31.4 (Fig. 2); change in the left mediastinum — diameter: 15 mm, SUV 32.1 (Fig. 3.)

In November 2011, the patient was admitted to the Division of Endocrinology, Silesian Medical University in Katowice. The test results indicated elevated concentration of chromogranin A — 26 U/L (norm 2–18), and after conducting a histopathological re- consultation of all the microscopic specimens, a final diagnosis was given, namely NEN G1 (WHO 2010), Ki-67 < 2%. Imaging examinations were scheduled.

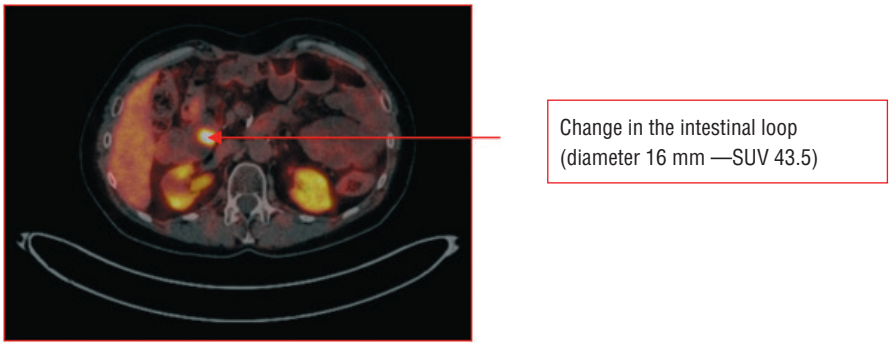


Figure 1. *Image of the ^{68}Ga-PET/CT scan shows expression of somatostatin receptors in change in the intestinal loop*
Rycina 1. *Badanie ^{68}Ga-PET/CT uwidaczniające ekspresję receptorów somatostatynowych pomiędzy pętlami jelita cienkiego*

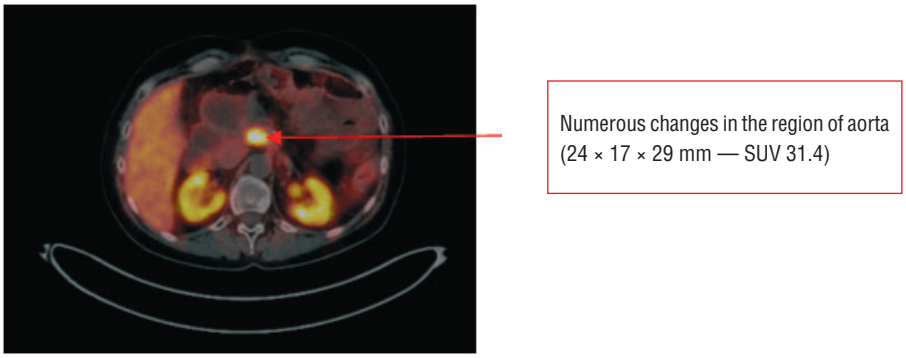


Figure 2. *Image of the ^{68}Ga-PET/CT scan shows expression of somatostatin receptors in numerous changes of region of aorta*
Rycina 2. *Badanie ^{68}Ga-PET/CT uwidaczniające ekspresję receptorów somatostatynowych w licznych zmianach ogniskowych okolicy aorty*

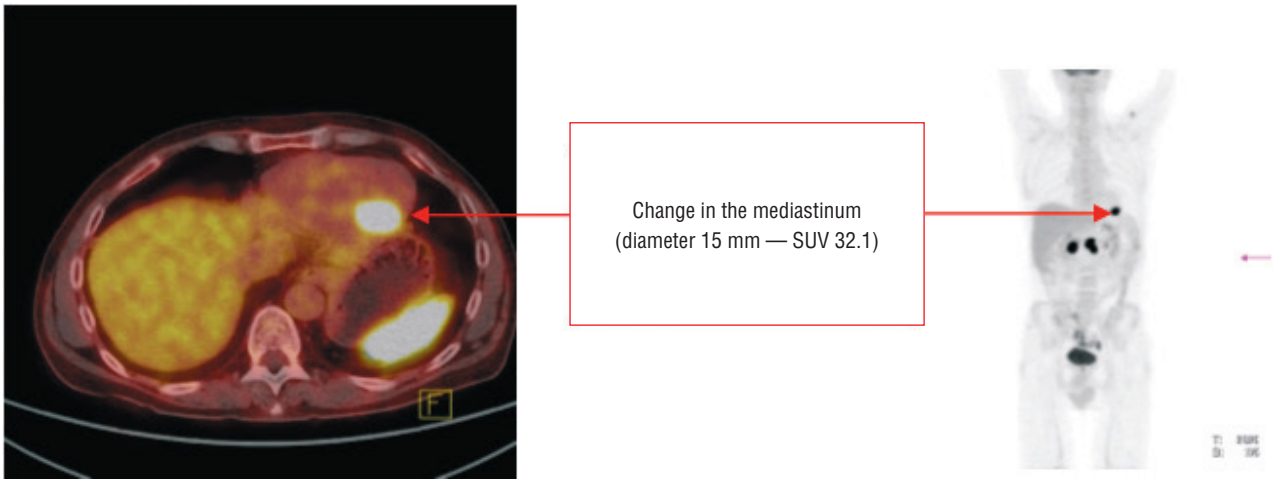


Figure 3. *Image of the ^{68}Ga-PET/CT scan shows expression of somatostatin receptors in mediastinum focus (reproduced with permission of L. Królicki, Department of Nuclear Medicine, Medical University, Warsaw)*
Rycina 3. *Badanie ^{68}Ga-PET/CT uwidaczniające ekspresję receptorów somatostatynowych w ognisku zlokalizowanym w śródpiersiu (opublikowane za pozwoleniem: L. Królicki, Zakład Medycyny Nuklearnej Akademii Medycznej w Warszawie)*

In April 2012, the patient was re-operated on in the Centre in Gdańsk. An exploratory laparotomy was performed, finding an irremovable recurrence of the tumour in the small intestine mesentery. In July 2012, a ^{68}Ga-PET/CT scan was performed, revealing changes in the aortic region (43 × 40 mm — SUV 18.3) and a new change (25 × 24 mm — SUV 12.5); a change in the mediastinum (diameter: 15 mm — SUV 22.7), and disease progression was detected (Fig. 4).

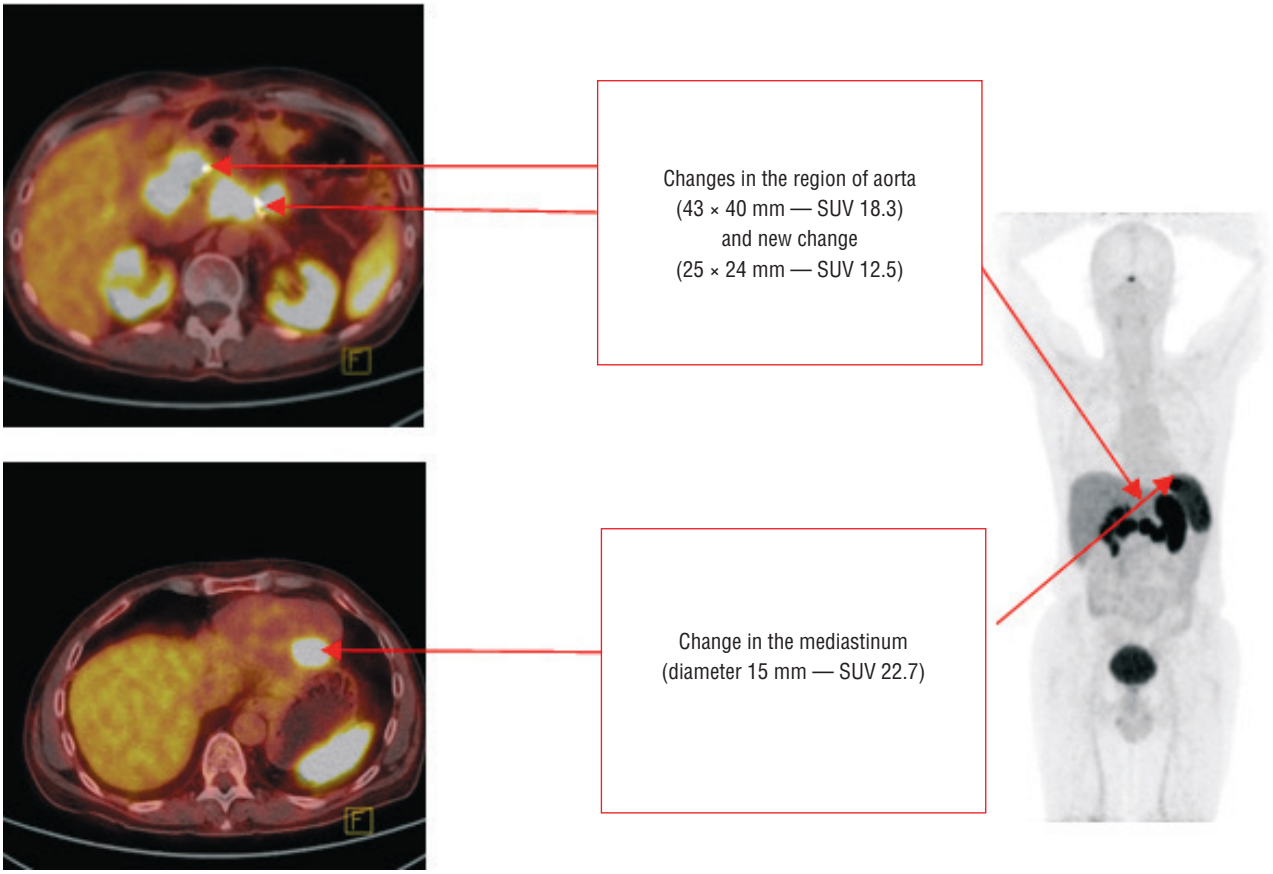
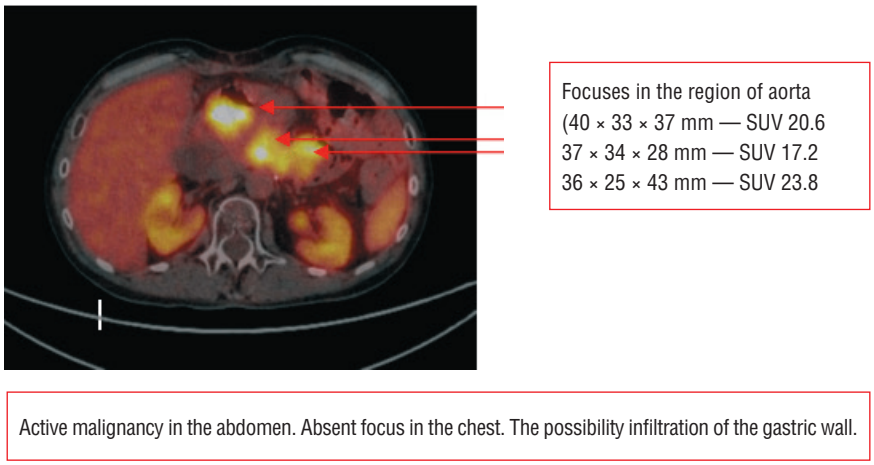


Figure 4. *Image of the ^{68}Ga-PET/CT scan shows expression of somatostatin receptors in numerous changes of region of aorta in the mediastinum (reproduced with permission of L. Królicki, Department of Nuclear Medicine, Medical University, Warsaw)*

Rycina 4. *Badanie ^{68}Ga-PET/CT uwidaczniające ekspresję receptorów somatostatynowych w licznych zmianach ogniskowych okolicy aorty oraz w zmianie ogniskowej zlokalizowanej w śródpiersiu (opublikowane za pozwoleniem L. Królicki, Zakład Medycyny Nuklearnej Akademii Medycznej w Warszawie)*

In September 2012, echocardiography was repeated, revealing a focus on the apical side wall of the left ventricle measuring 24 mm in diameter. The patient was admitted to the Department of Cardiac and Vascular Surgery in Gdańsk for surgical treatment of a left ventricular tumour. In December 2012, the tumour from the left ventricle of the heart was excised, followed by Dacron patch implantation. Histopathological consultation indicated the following: metastasis neoplasm NEN G2 (Ki-67 4%); size 3 × 2.3 × 1.5 cm with immunohistochemical expression of synaptophysin and CD56. In December 2012, a ^{68}Ga-PET/CT scan was performed, revealing an active malignancy in the abdomen, the possibility of infiltration into the gastric wall as well as three foci in the aortic region — 40 × 33 × 37 mm — SUV 20.6, 37 ×34 × 28 mm — SUV 17.2, 36 × 25 × 43 mm — SUV 23.8 (Fig. 5).

Treatment with everolimus at a dose of 10 mg per day was commenced. In March 2013, an abdominal MRI showed a pathological structure (24 mm) in the site of the removed pancreas and a focus in the duodenojejunal region (37 mm). The follow-up ^{68}Ga-PET/CT scan, which was performed in June 2013, revealed a regression in the size of the lesions, with overexpression of somatostatin receptors. Only two lesions were visible: a change in the head of the pancreas, measuring 20 × 25 × 20 mm, SUV 20.9 and a change in the aortic region, measuring 42 × 29 × 43 mm, SUV 17.5. In a follow-up MR imaging examination in September 2013, the changes in the site after pancreas removal and in the projection of the duodenojejunal flexure looked the same. The patient continues treatment with everolimus and somatostatin analogue. The general condition of the patient is good. For 1.5 years, the patient has been having approximately ten loose stools per day. Apart from that, the patient has been exhibiting no other symptoms of the disease. The ongoing treatment is well tolerated, and the concentrations of hormones, neuroendocrine tumour markers and parameters of calcium–phosphorus homeostasis are within normal ranges.



Rycina 5. *Image of the ^{68}Ga-PET/CT scan shows expression of somatostatin receptors in numerous changes of region of aorta in the mediastinum*

Rycina 5. *Badanie ^{68}Ga-PET/CT uwidaczniające ekspresję receptorów somatostatynowych w licznych zmianach ogniskowych okolicy aorty*

Discussion

In principle, each malignant tumour can metastasise to the heart. Only tumours of the central nervous system have not been proven to develop cardiac metastases. The most common neoplasms that metastasise to the heart include lung cancer, breast cancer and oesophageal cancer, leukaemia and malignant melanoma [15, 16]. Tumour cells can metastasise to the heart and pericardium by one of four different pathways: lymphatic, haematogenous, direct extension, or intracavitary diffusion through either the inferior vena cava or the pulmonary veins. Cardiac metastases are usually small and multiple. Single metastases are more frequently found in the right side of the heart than in the left. Most cases are characterised by diffuse bilateral spread. Metastases are most frequently located in the pericardium than in the myocardium, and most rarely in the endocardium. Intracavitary growth of secondary heart tumours is very rare [15, 16]. In the overwhelming majority of cases, cardiac metastases are diagnosed in patients with advanced disease, with the heart being one of many organs affected by metastasis. This is because their size principally remains clinically silent and the patients predominantly manifest general cancer cachexia. As a result, cardiac metastases are often found only after a patient's death during a post-mortem examination [15]. The clinical symptoms of cardiac metastases, depending on their locality and size, may differ to a great extent, ranging from a slight shortness of breath and tachycardia to cardiac arrhythmias leading to sudden cardiac death, or symptoms of acute tamponade.

In the case described, the cardiac metastasis of the pNET was detected in the course of generalised disease in the form of lymph node metastases and local recurrence. The metastasis to the wall of the left ventricle occurred through lymphatic pathways. However, it was a single pathway, which is rarely detected. The patient manifested no clinical symptoms of the metastasis in the left ventricular wall. Intravital diagnosis of asymptomatic cardiac metastases is not frequent. There are no specific laboratory tests for the diagnosis of cardiac metastases. Myocardial metastases are known to be a possible cause of moderate elevation of cardiac troponin [17]. Irregularities detected on physical examination and by electrocardiography depend on the location of the metastases. Physical examination and ECG revealed no irregularities in the patient concerned. The CT and MR are imaging techniques, with various sensitivity depending on the size of metastases and their location. The method of choice for the detection of cardiac metastases is two-dimensional echocardiography [18]. In the patient described, the cardiac lesion was first found in the ^{68}Ga-PET/CT scan in January 2010. Despite repeated echocardiography tests, it was only in September 2012 that an abnormal echocardiogram was detected. The great role of somatostatin analogue receptor PET imaging in patients with highly differentiated endocrine tumours of the gastrointestinal system is well known [4, 11]. It is estimated that the sensitivity, specificity and accuracy of the ^{68}Ga-PET/CT scan in these patients amount to 97%, 92% and 96% respectively [19]. The case of our patient indicates that the enormous significance of the ^{68}Ga-PET/CT scan in highly differentiated endocrine tumours of the gastrointestinal system is independent of the location of the lesions.

There is no standard treatment for cardiac metastases. Because, in the overwhelming majority of patients,

such metastases are diagnosed in the course of the disease with multiple metastases to numerous organs, a systemic treatment is used wherever possible. Cardiac and circulatory symptoms are alleviated by pharmacological methods. Prognosis for these patients is very unfavourable and surgical resection is indicated only in exceptional cases. Radical resection is often unsuccessful and the post-operative mortality rate is high. In the case described, the detected cardiac metastasis was of a single type and despite the diagnosis of an advanced disease and lack of cardiac symptoms, a decision was made to perform a surgical removal of the metastatic tumour from the heart. The procedure consisted in total removal of the irregular mass from the wall of the left ventricle and the subsequent histopathological examination confirmed the presence of PNEN tissue. The removal of the tumour helped prevent the occurrence of cardiac and circulatory symptoms, including sudden cardiac death.

Another treatment method for cardiac metastases is radiation therapy. However, this method may lead to pulmonary and myocardial fibrosis resulting in disturbances of the conduction system and pericarditis. The efficacy of radiation therapy depends not only on the locality of the lesions but also on the type of tumour cells. The recommendations for PNENs treatment do not propose radiation therapy [4, 8].

Because the cardiac metastasis was confirmed in the course of generalised, progressing disease, systemic therapy remains the basic method of treatment. In the treatment of both secreting and non-secreting PNENs, a significant role is played by somatostatin analogues (SSA). The antiproliferative effect of SSA, tending to be spectacular in some case studies, was confirmed in phase III trials [4, 20]. In the patient described, further symptomatic progression was confirmed earlier during SSA therapy, which results in a single SSA therapy not being the target one. The chemotherapy used earlier was not effective either. A new treatment option for PNENs is the application of molecularly targeted agents [4, 8]. Sunitinib, which is a multi-target receptor kinase inhibitor, and everolimus, which is a mammalian target of rapamycin inhibitor, are registered for the treatment of advanced PNENs, with progression of the disease following chemotherapy [21, 22]. The patient was started on sunitinib and continues the SSA therapy. The tolerance of the ongoing treatment has been very good; the patient suffered no side effects from the administered drug. Test results indicate that the metastases have been reduced in size and no other sites of the disease have been found.

This report describes a case of a ten-year course of the disease, including an eight-year treatment of metastatic condition. Only one case of a PNEN patient with cardiac metastasis has been described to date [14]. In contrast to that patient, ours received successful post-operative treatment due to cardiac metastasis.

Summing up, the application of various methods of treatment, not excluding cardiosurgical operations, in patients with generalised pancreatic neuroendocrine tumour with low proliferative potential, offers patients the chance to prolong their survival and maintain a good quality of life.

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