Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 63; Numer/Number 1/2012
ISSN 0423–104X

A non-functioning pancreatic neuroendocrine tumour: a case report

Nieczynny hormonalnie nowotwór neuroendokrynny trzustki: opis przypadku klinicznego

Violetta Rosiek[1], Jolanta Kunikowska[2], Beata Kos-Kudła[1]

[1]Division of Endocrinology, Department of Pathophysiology and Endocrinology, Silesian Medical University, Katowice, Poland
[2]Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland

Abstract

We present the diagnostic and therapeutic difficulties encountered in a patient with a clinically advanced pancreatic neuroendocrine tumour. The report concerns a 60-year-old female patient with the diagnosis of non-functioning pancreatic neuroendocrine tumour (NET G1) with liver, peripancreatic lymph node and mediastinal metastases. Due to the presence of advanced disease (inoperable pancreatic tumour, presence of multiple metastases) the patient was considered ineligible for surgical treatment on two occasions. Tissue samples for histopathology were collected during an exploratory laparotomy, which made it possible to establish the diagnosis. As somatostatin receptor scintigraphy was positive, the patient was started on somatostatin analogues and radionuclide therapy was initiated, resulting in satisfactory response in the form of complete remission of liver metastases and the decreased size of the primary tumour in the pancreas. The use of somatostatin analogues in the case of an inoperable neuroendocrine tumour which was assessed as clinically advanced, yet possessing a low proliferative potential, is a promising therapeutic option. **(Pol J Endocrinol 2012; 63 (1): 59–64)**

Key words: *pancreatic neuroendocrine tumour, somatostatin analogue, radionuclide therapy*

Streszczenie

W pracy przedstawiono trudności diagnostyczno-terapeutyczne u pacjentki z zaawansowanym klinicznie nowotworem neuroendokrynnym trzustki. Opisano przypadek 60-letniej chorej z rozpoznanym nieczynnym hormonalnie nowotworem neuroendokrynnym trzustki (NET G1), z przerzutami do wątroby i węzłów chłonnych okołotrzustkowych i śródpiersia. Ze względu na zaawansowanie choroby (nieresekcyjny guz trzustki, obecność licznych przerzutów) chorą zdyskwalifikowano 2-krotnie z leczenia operacyjnego. Podczas laparotomii zwiadowczej pobrano materiał do badania histologicznego, co pozwoliło na ustalenie rozpoznania. W scyntygrafii receptorowej potwierdzono obecność receptorów somatostatynowych, włączono leczenie analogami somatostatyny oraz zastosowano leczenie radioizotopowe. W wyniku zastosowanej terapii uzyskano zadowalający efekt w postaci całkowitej regresji zmian przerzutowych w wątrobie oraz zmniejszenia wymiarów guza trzustki.
Zastosowanie analogów somatostatyny w przypadku nieoperacyjnego, zaawansowanego klinicznie, jednak o niskim potencjale proliferacyjnym, nowotworu neuroendokrynnego trzustki, stanowi obiecującą opcję terapeutyczną. **(Endokrynol Pol 2012; 63 (1): 59–64)**

Słowa kluczowe: *nowotwór neuroendokrynny trzustki, analog somatostatyny, leczenie radioizotopowe*

Introduction

Non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs) account for 60–80% of all pancreatic neuroendocrine neoplasms, while the latter make up 2–10% of all pancreatic tumours [1–3]. According to the latest World Health Organisation (WHO) classification, adopted in 2010, the following groups of neuroendocrine tumours in terms of grading are distinguished:

— Neuroendocrine tumour G1 (NET G1);
— Neuroendocrine tumour G2 (NET G2);
— Neuroendocrine carcinoma (NEC);
— Mixed adenoneuroendocrine carcinoma (MANEC) [4].

The manifestations of neuroendocrine tumours develop late and are associated with locally advanced disease, which is usually already quite considerable, and with distant metastases. The primary tumour is most commonly located in the head of the pancreas and is large (> 50 mm). The incidence peaks in the fifth decade of life and both sexes are equally affected [3]. The usual symptoms include abdominal pain, weight loss, loss of appetite, nausea, and vomiting [3, 5, 6]. Due to the heterogenic nature of the tumour, and the generally considerable advancement of the disease process at diagnosis, the decisions regarding the diagnostic evaluation and optimal treatment require extensive experience and collaboration between various

Violetta Rosiek MD, Division of Endocrinology, Department of Pathophysiology and Endocrinology, Silesian Medical University, ul. Ceglana 35, 40–952 Katowice, Polska, tel/fax: +48 32 358 13 66, e-mail: vml@wp.pl

specialists, including an endocrinologist, a gastroenterologist, a surgeon, an oncologist and nuclear medicine specialists.

Case presentation

A 60-year-old female patient with the diagnosis of a pancreatic neuroendocrine tumour was admitted in September 2008 to the Department of Endocrinology, Silesian Medical University, Katowice, Poland, for further diagnostic evaluation with a view to establishing the optimal management.

For the previous two years, she had been experiencing asthaenia and epigastric pain. Gastrointestinal endoscopic studies (an upper GI endoscopy and a colonoscopy) carried out in June 2007 revealed erosive gastroduodenitis with Helicobacter pylori infection. Despite eradication treatment, the abdominal pain persisted. An abdominal ultrasound performed in July 2008 revealed a tumour in the pancreatic head measuring 34 × 24 mm and several masses in the liver (most probably of metastatic nature). An abdominal CT scan confirmed the presence of a pancreatic head tumour measuring 55 × 47 mm (Figure 1) and six metastatic masses in the liver (with the largest one measuring 23 mm in diameter) (Figure 2).

The patient was referred to the Department of Surgery and underwent an exploratory laparotomy which revealed an inoperable pancreatic tumour, and during which tissue samples for histopathology were collected from the metastatic masses in the liver and the peripancreatic lymph nodes.

The histopathologic examination revealed well-differentiated neuroendocrine neoplasm of the pancreas with metastatic spread to the liver and lymph nodes (chromogranin(+), synaptophysin(+), proliferation index Ki67 1%.

In September 2008, during hospitalisation at the Department of Endocrinology, the concentrations of neuroendocrine tumour markers were within reference ranges: 5.9 ng/24 h and 2.83 ng/24 h for 5-hydroxyindoleacetic acid (5-HIAA) in two 24-hour urine collections, respectively (reference range: 2–6 ng/24 h); 31.66 U/l for chromogranin A (reference range: 2–18 IU/l); 46.0 μIU/l for gastrin (reference range: 28–185 μIU/l) and 137.4 ng/ml for serotonin (reference range: 40–400 ng/ml). Other hormone assessments were also performed, which ruled out multiple endocrine neoplasia type 1 (MEN 1). A chest CT scan revealed multiple subpleural nodules in both lungs and mediastinal lymph nodes of borderline sizes.

A decision against performing biopsies of these lesions was made due to the presence of numerous emphysematous bullae. The patient refused to undergo a mediastinoscopy. Somatostatin receptor scintigraphy (SRS) using 99mTc-Tectrotide revealed pathological accumulation of the tracer in the head of the pancreas and in five masses in the liver. No expression of somatostatin receptors (SSTRs) was demonstrated in the nodules identified in the lungs. Based on the confirmation of the presence of SSTRs in the pancreatic tumour and in the liver, the patient was started on a long-acting somatostatin analogue, Somatuline Autogel 90 mg every 28 days, in September 2008.

After three doses of the drug, the abdominal symptoms decreased and the follow-up CT scan in January 2009 revealed no changes in the pulmonary nodules and mediastinal lymph nodes, and a considerable regression

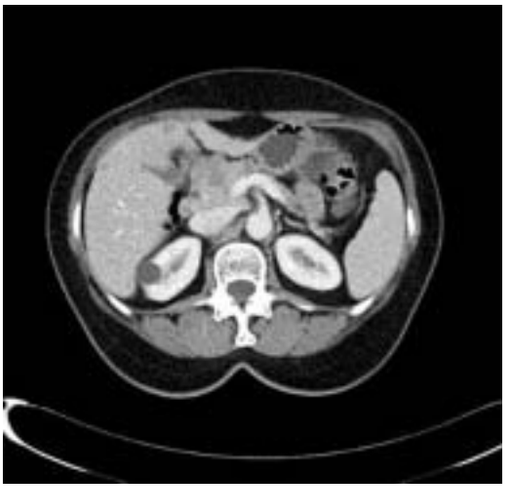

Figure 1. *Abdominal computed tomography (CT) scan: a pancreatic head tumour measuring 55 × 47 mm*

Rycina 1. *Tomografia komputerowa (CT) jamy brzusznej: guz głowy trzuski, wymiar 55 × 47 mm*

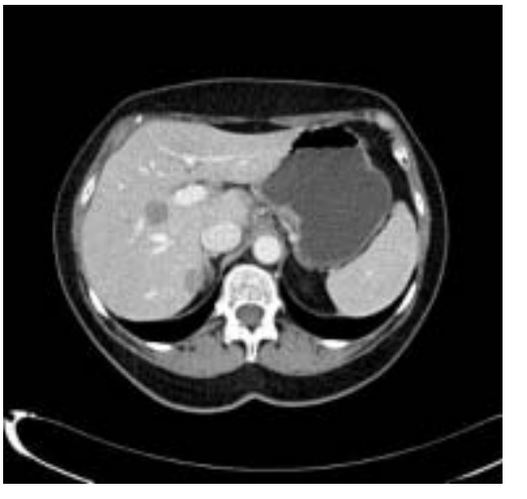

Figure 2. *Abdominal computed tomography (CT) scan: liver metastases (with the greatest mass measuring 23 mm in diameter)*

Rycina 2. *Tomografia komputerowa (CT) jamy brzusznej: przerzuty do wątroby (maks. 23 mm)*

of the pancreatic head tumour (30 mm in diameter) with the presence of radiologic atrophic changes and only two metastatic masses in the liver. Serum concentrations of neuroendocrine tumour markers were still within reference ranges. The patient was given a recommendation to continue treatment with Somatuline Autogel at the dose of 120 mg.

Following the next three doses, in March 2009, a follow-up abdominal ultrasound scan revealed a decrease in the number and sizes of the liver metastases and in the size of the pancreatic head tumour. The patient's performance status remained good and her only complaints were hot flushes. There was only a slight increase in 5-HIAA levels in 24-hour urine collection accompanied by normal levels of CgA and serotonin. Treatment with the long-acting somatostatin analogue was continued, and in August 2009 the patient underwent a positron emission tomography (PET) scan using somatostatin analogues labelled with gallium-68 (68Ga-DOTA-TATE PET/CT), which makes it possible to assess the primary (Figure 3) and metastatic masses (Figure 4), particularly in the case of well-differentiated neuroendocrine tumours [7–9].

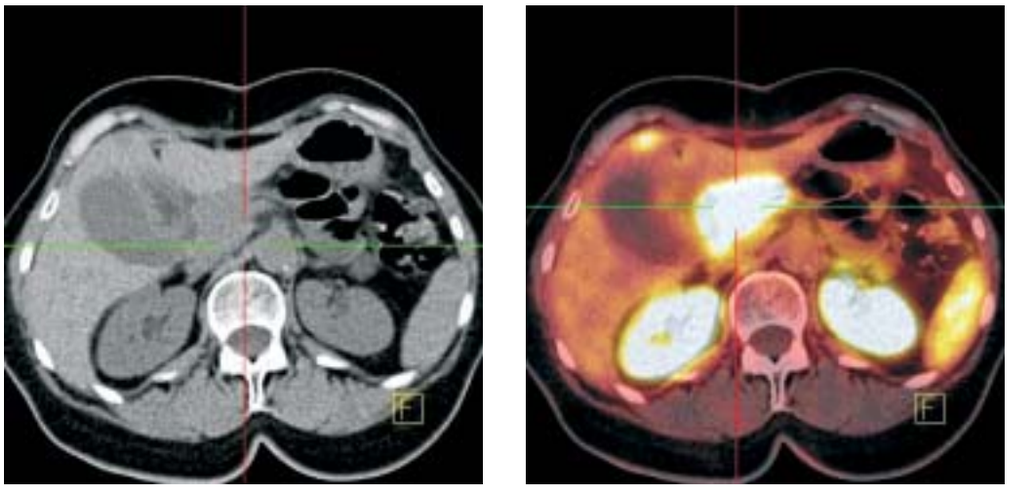

Figure 3. *Hybrid imaging positron emission tomography with computed tomography using ^{68}Ga-DOTATATE (^{68}Ga-DOTA-TATE PET/CT): 43 × 32 mm an extensive tumourous mass with calcificationthe in the head of the pancreas, with overexpression of somatostatin receptors*

Rycina 3. *Badanie pozytonowej tomografii emisyjnej z wykorzystaniem analogów somatostatyny znakowanych galem 68 (^{68}Ga-DOTATATE PET/CT): głowa trzustki — rozległa zmiana guzowata ze zwapnieniem o wymiarach 43 × 32 mm ze zwiększoną ekspresją receptorów*

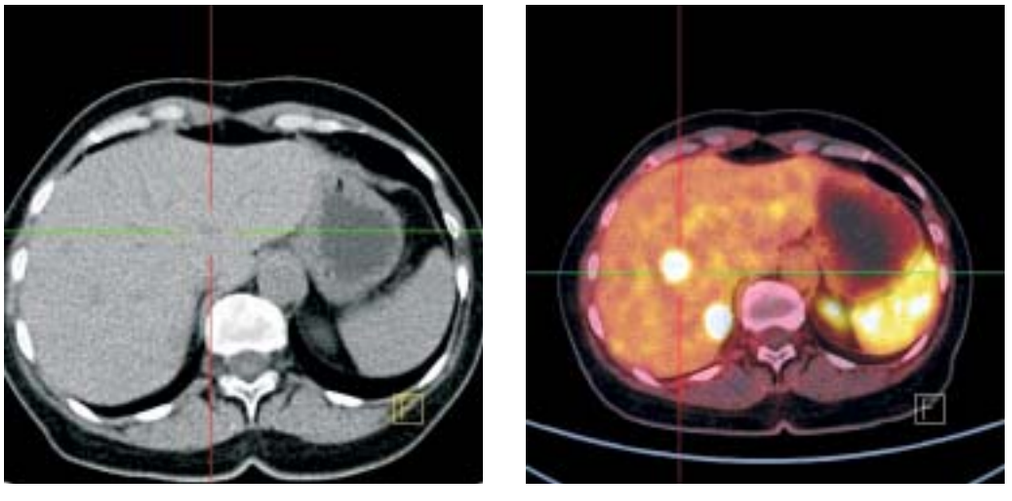

Figure 4. *Hybrid imaging positron emission tomography with computed tomography using ^{68}Ga-DOTATATE (^{68}Ga-DOTA-TATE PET/CT): the liver — a lots of liver metastases showing overexpression of somatostatin receptors*

Rycina 4. *Badanie pozytonowej tomografii emisyjnej z wykorzystaniem analogów somatostatyny znakowanych galem 68 (^{68}Ga-DOTATATE PET/CT): wątroba — liczne ogniska ze zwiększoną ekspresją receptorową w wątrobie*

The scans performed at the Department of Nuclear Medicine revealed areas of somatostatin receptor overexpression within the pancreatic head mass, liver masses and the right superior paratracheal lymph nodes. Given the disseminated nature of the disease and good expression of somatostatin receptors, the patient was referred for radionuclide therapy with radiolabelled somatostatin analogues.

During the repeat surgical consultation, the patient was again considered ineligible for surgery. The patient's condition was stable and she complained of occasional hot flushes and epigastric symptoms. No increase in neuroendocrine tumour markers was observed. The patient continued treatment with the somatostatin analogue, Somatuline Autogel, at the dose of 120 mg every 28 days. A subsequent ^{68}Ga-DOTA-TATE PET/CT scan performed in February 2010 did not reveal any new masses that would exhibit somatostatin receptor overexpression (Figures 5, 6).

The patient was considered eligible for radionuclide therapy and received four cycles of ^{90}Y-DOTA-TATE between April and August 2010 and one cycle of

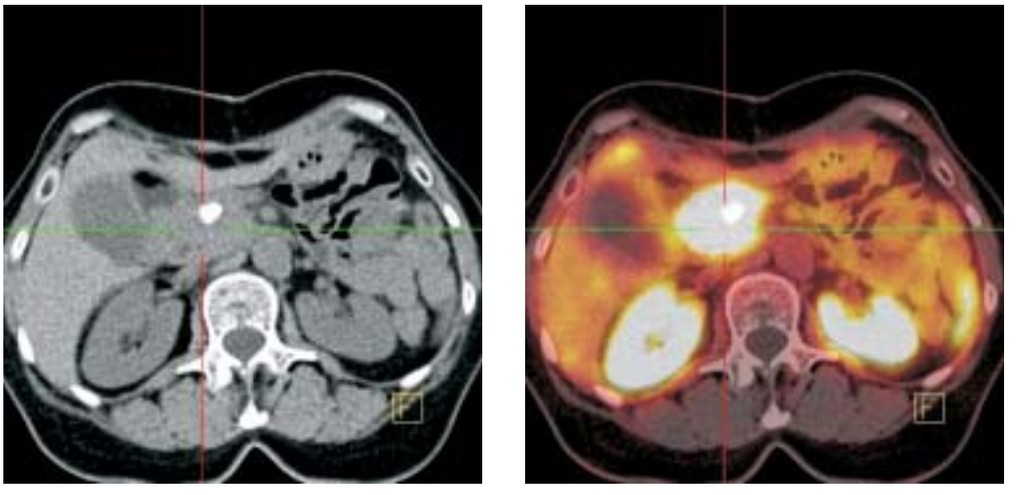

Figure 5. *Hybrid imaging positron emission tomography with computed tomography using ^{68}Ga-DOTATATE (^{68}Ga-DOTA-TATE PET/CT): the head of the pancreas — an extensive tumourous mass with calcification of the same sizes as in the previous scan, with overexpression of somatostatin receptors*

Rycina 5. *Badanie pozytonowej tomografii emisyjnej z wykorzystaniem analogów somatostatyny znakowanych galem 68 (^{68}Ga-DOTATATE PET/CT): głowa trzustki — rozległa zmiana guzowata ze zwapnieniem o wymiarach jak poprzednio, ze zwiększoną ekspresją receptorów*

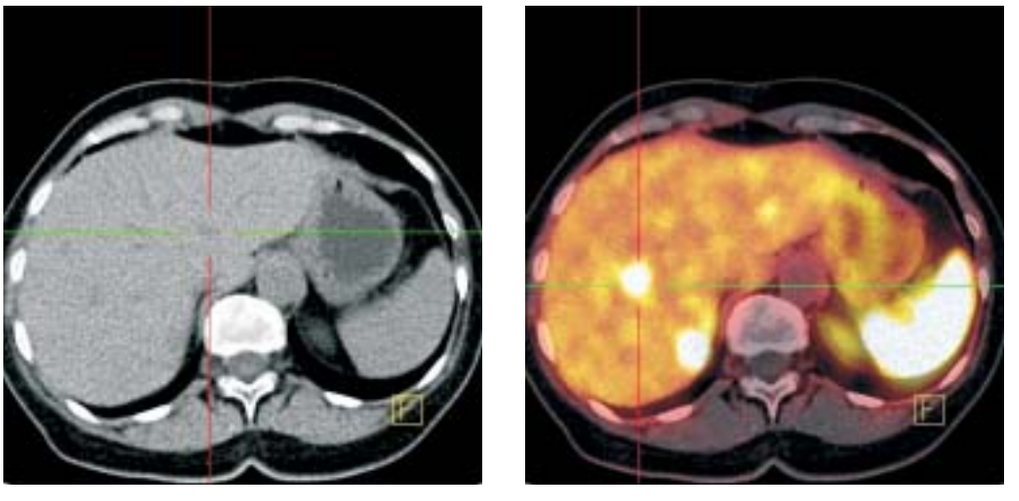

Figure 6. *Hybrid imaging positron emission tomography with computed tomography using ^{68}Ga-DOTATATE (^{68}Ga-DOTA-TATE PET/CT): the liver — a lots of liver mestastees showing overexpression of somatostatin receptors, with the largest one in segment 5/8*

Rycina 6. *Badanie pozytonowej tomografii emisyjnej z wykorzystaniem analogów somatostatyny znakowanych galem 68 (^{68}Ga-DOTATATE PET/CT): wątroba — liczne ogniska ze zwiększoną ekspresją receptorową w wątrobie, największe w segmencie 5/8*

^{177}Lu-DOTA-TATE. The complications of the radionuclide therapy included secondary pancytopenia. The follow-up imaging studies (abdominal CT and somatostatin receptor scintigraphy) performed after completion of the radionuclide therapy showed satisfactory response in the form of complete remission of liver metastases and the decreased size of the primary tumour in the pancreas. For the third time, surgery is now being considered, provided that the patient's blood counts return to normal.

Discussion

The outcomes of treatment of pancreatic neuroendocrine tumours largely depend on the stage of the disease at diagnosis. In order to determine the location and size of the primary tumour, and to detect metastases, imaging studies need to be performed [10].

The imaging modalities include computed tomography, magnetic resonance imaging, ultrasound, somatostatin receptor scintigraphy and PET/CT using somatostatin analogues labelled with gallium-68 [11]. The use of modern diagnostic methods, particularly endoscopic ultrasound (EUS), considerably improves the chances of early detection. The sensitivity of the method is 90–100% for tumours located in the head and body of the pancreas, and 75–80% for peripheral tumours. A normal picture of the pancreas in EUS practically rules out the presence of a tumour. The diagnosis of the disease is based on histopathology results. A biopsy during an EUS scan is performed if the tumour renders the patient ineligible for surgery. The sensitivity and specificity of EUS combined with a biopsy, as far as the diagnosis of neuroendocrine tumours is concerned, are 84% and 92.5%, respectively [3, 12].

Pancreatic neuroendocrine tumours are generally detected late (which was the case with our patient), often at a very advanced stage (T2N1M1), despite the well-differentiation of the tumour and a low proliferation index (neuroendocrine tumour G1 [NET G1] according to the WHO classification adopted in 2010). In our patient, the imaging studies (ultrasound, CT) of the abdominal cavity revealed a tumour in the head of the pancreas and liver metastases. The patient was being considered for surgery with a diagnosis of suspected adenocarcinoma of the pancreas, but the tumour was considered unresectable having taken into account the disseminated nature of the disease. The correct diagnosis, one of a neuroendocrine tumour, was established later, based on a histopathologic examination of tissue samples collected during an exploratory laparotomy.

Radical resection of the primary tumour, if possible — is the mainstay of treatment in pancreatic neuroendocrine tumours. The location and stage of the tumour determine the type and extent of the surgical tumour resection [13]. In tumours which are located in the head of the pancreas and which measure more than 3 cm in diameter, resection of the neighbouring organs is also recommended. If liver metastases are present, which is the case in 59–80% of patients at diagnosis, a synchronous or metachronous resection of the primary tumour and the metastatic masses is recommended. Aggressive surgical treatment increases five-year survival rates in these patients from 46% to 63% (or, according to other authors, to 83%). In specialised liver surgery centres, it is possible to combine different techniques, such as resection of metastatic masses, ablation, embolisation or chemoembolisation of hepatic arteries [4, 13–16].

In the case of our patient, two national reference centres for surgery determined inoperability of the lesions due to the presence of advanced disease (unresectable pancreatic tumour, multiple liver and lymph node metastases, suspected lung metastases) and the involvement of the portal circulation. During the explorative laparotomy, tissue samples from the masses located in the liver and the surrounding lymph nodes were collected, which made it possible to correct the previous misdiagnosis. A decision was then made to initiate treatment with a long-acting somatostatin analogue, which shows antiproliferative properties (though not yet proved in randomised studies on the pancreas), cytotoxic and cytostatic properties, leading to stabilisation of tumour growth [17].

Exerting direct effects through somatostatin receptors [18] and indirect effects by suppressing the activity of growth factors, suppressing angiogenesis and exerting immunomodulatory action, results in a stabilising effect on tumour growth and limits the development of metastases. Stabilisation of the disease can be achieved in 24–57% of patients. Studies also show that tumour regression can also be achieved in a small percentage of patients (3–9%) [3, 19, 20, 21].

Several months of treatment with the somatostatin analogue gave a very satisfactory result: a decrease in the primary tumour size and a decrease in the number and sizes of the liver metastases. Given the overexpression of somatostatin receptor in the tumour, confirmed by scintigraphy, the patient received radionuclide therapy with radiolabelled somatostatin analogues on top of somatostatin treatment. Remissions following this treatment are confirmed by clinical studies of ^{90}Y-DOTA-TOC, ^{177}Lu-DOTA-TATE, ^{90}Y-DOTA-TATE, which showed that this treatment was able to reduce tumour mass and bring about stabilisation of the disease [3, 17, 19, 22–24].

In the case of our patient, non-surgical treatments resulted in a marked clinical improvement, regression

of the disease accompanied by a decrease in pancreatic tumour mass, and a complete remission of liver metastases.

In conclusion, the use of somatostatin analogues in an unresectable, clinically advanced neuroendocrine tumour, yet exhibiting a low proliferative potential, is a promising therapeutic option.

References

1. Falconi M, Plockinger U, Kwekkeboom DJ et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006; 84: 196–211.
2. O'Toole D, Salazar R, Falconi M at al. Rare functioning pancreatic endocrine tumors. Neuroendocrinology 2006; 84: 189–195.
3. Kos-Kudła B, Telega A. Nieczynne hormonalnie guzy endokrynne trzustki. W: Beata Kos-Kudła, red. Guzy neroendokrynne układu pokarmowego. Via Medica, Gdańsk 2010; 261–274.
4. Klimstra DS, Modlin IR, Coppola D et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010; 39: 707.
5. O'Grady HL, Conlon KC. Pancreatic neuroendocrine tumors. Eur J Surg Oncol 2008; 34: 324–332.
6. Anlauf M, Sipos B, Kloppel G. Tumors of endocrine pancreas. Pathologe 2005; 26: 46–51.
7. Sundin A, Vullierme MP, Kaltsas G et al. ENETS Guidelines for the Standards of Care in Patients with Neuroendocrine Tumours: radiological examinations in patients with neuroendocrine tumours. Neuroendocrinology 2009; 90: 167–183.
8. Ruf J, Heuck F, Schiefer J et al. Impact of multiphase 68 Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors. Neuroendocrinology 2010; 91: 101–109.
9. Czepczyński R, Wygoda Z, Sowiński J. Pozytronowa tomografia emisyjna w guzach neuroendokrynnych. W: Beata Kos-Kudła, red. Guzy neroendokrynne układu pokarmowego. Via Medica, Gdańsk 2010; 77–89.
10. Królikowski L, Kunikowska J. Obrazowanie guzów neuroendokrynnych. W: Beata Kos-Kudła, red. Guzy neroendokrynne układu pokarmowego. Via Medica, Gdańsk 2010; 54–62.
11. Kos-Kudła B, Matyja V, Telega A. Diagnosis and therapy of gastrointestinal neuroendocrine tumors. Part 2. Management guidelines for foregut tumors (endocrine tumors of the stomach, duodenum and pancreas) according to guidelines recommended by the Polish Network of Neuroendocrine Tumors. Onkologia Info 2008; 5: 212–218.
12. Alsohaibani F, Bigam D, Kneteman N et al. The impact of preoperative endoscopic ultrasound on the surgical management of pancreatic neuroendocrine tumours. Can J Gastroenterol 2008; 22: 817–820.
13. Lampe P, Jabłońska B. Postępowanie chirurgiczne w guzach neuroendokrynnych. W: Beata Kos-Kudła, red. Guzy neroendokrynne układu pokarmowego. Via Medica, Gdańsk 2010; 77–89.
14. Franko J, Feng W, Yip L et al. Nonfunctional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. J Gastrointest Surg 2010; 14: 541–548.
15. Liu DM, Kennedy A, Turner D et al. Minimally invasive techniques in management of hepatic neuroendocrine metastatic disease. Am J Clin Oncol 2009; 32: 200–215.
16. Hill JS, McPhee JT, McDade TP et al. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer 2009; 115: 741–751.
17. Kos-Kudła B. The treatment of neuroendocrine tumors (NET) with somatostatin analogs. W: Pawlikowski M, red. Somatostatin analogs in diagnostics and therapy. Landes Bioscience 2007, 57–67.
18. Kumar U, Grant M. Somatostatin and somatostatin receptors. Results Probl Cell Differ 2010; 50: 137–184.
19. Kos-Kudła B, Bolanowski M, Handkiewicz-Junak D et al. Diagnostic and therapeutic guidelines for gastrointestinal neuroendocrine tumors (recommended by the Polish Network of Neuroendocrine Tumors). Endokrynol Pol 2008; 59: 41–56.
20. Grozinsky-Glasberg S, Shimon I, Karbonits M et al. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanism. Endoc-Related Cancer 2008; 15: 701–720.
21. Dębski MG, Makowska A, Bar-Andziak E. Insulinoma in a patient with MEN 1 syndrome — 9-year follow-up: case report. Endokrynol Pol 2010; 61: 212–216.
22. Kwekkeboom DJ, Mueller-Brand J, Paganelli G et al. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J Nucl Med Mol Imaging 2003; 30: 417–422.
23. Cwikla JB, Sankowski A, Seklecka N et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol 2010; 21: 787–794.
24. Sowa-Staszczak A, Pach D, Kunikowska J et al. Efficacy and safety of 90Y-DOTATATE therapy in neuroendocrine tumors. Endokrynol Pol 2011; 62: 392–400.