Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 60; Numer/Number 5/2009
ISSN 0423–104X

Long-term survival and nearly asymptomatic course of carcinoid tumour with multiple metastases (treated by surgery, chemotherapy, ^{90}Y-DOTATATE, and LAR octreotide analogue) — a case report

Długotrwałe przeżycie i niemal bezobjawowy przebieg rakowiaka z mnogimi przerzutami (leczonego metodą chirurgiczną, chemioterapią, ^{90}Y-DOTATATE i analogiem oktreotydu LAR) — opis przypadku

Marcin Kałużny[1], Marek Bolanowski[1], Małgorzata Sukiennik-Kujawa[2], Piotr Ponikowski[2], Daria Handkiewicz-Junak[3], Barbara Jarząb[3], Aleksandra Jawiarczyk[1], Joanna Syrycka[1]

[1]*Department of Endocrinology, Diabetology and Isotope Therapy, Medical University, Wroclaw*
[2]*Department of Cardiology, 4 Military Hospital, Wroclaw*
[3]*Department of Nuclear Medicine and Endocrine Oncology, Cancer Centre Maria Sklodowska-Curie Memorial Institute, Gliwice*

Abstract

Carcinoids are the most common neuroendocrine tumours. They are usually slowly growing, located in the small intestine, secrete serotonin, and are characterized by long survival of patients, so prognosis is generally good. The most frequently encountered clinical presentations of carcinoids are intermittent abdominal pain and carcinoid syndrome (diarrhoea and flushing). Metastases worsen the prognosis and limit the survival of the patients. We report a case of carcinoid tumour with primary focus in the ileum, with an appendix infiltration, in a thirty-two-year-old woman with acute appendicitis symptoms only. Carcinoid was diagnosed postoperatively by histopathological examination. Nowadays, twenty-five years after the surgery, there is evidence of nearly asymptomatic numerous metastases. Only intermittent abdominal pain for about 1–2 years was reported. Partial metastases resection was performed, followed by chemotherapy, ^{90}Y-DOTATATE and then long-acting release octreotide analogue therapy. In the meantime, severe chronic heart failure (NYHA IV) due to tricuspid combined valvular heart disease and pulmonary hypertension was diagnosed. Combined therapy, typical for chronic heart failure, together with long-acting octreotide analogue highly improved the patient's heart sufficiency and reduced carcinoid syndrome symptoms. The only adverse events of octreotide therapy were hyperbilirubinaemia and itching. Long-term survival is typical for carcinoids, but 30-years survival has not been described in the literature yet. **(Pol J Endocrinol 2009; 60 (5): 401–406)**

Key words: *carcinoid, octreotide, chronic heart failure*

Streszczenie

Rakowiak jest jednym z najczęstszych guzów neuroendokrynnych. Umiejscawia się w obrębie jelita cienkiego, zazwyczaj jako wolno rosnący guz wydzielający serotoninę. Pacjentów chorych na rakowiaka charakteryzuje długie przeżycie i dobre w większości przypadków rokowanie. Najczęstszymi objawami tego nowotworu są nawracające bóle w jamie brzusznej i objawy zespołu rakowiaka (biegunka i napadowe zaczerwienienia skóry — „flush"). Pojawienie się przerzutów pogarsza rokowanie oraz skraca czas przeżycia chorych. Opisany przypadek dotyczy 32-letniej kobiety z pierwotnym ogniskiem rakowiaka zlokalizowanym w jelicie krętym, naciekającym wyrostek robaczkowy z objawami ostrego zapalenia wyrostka robaczkowego. Rakowiak został zdiagnozowany pooperacyjnie na podstawie oceny histopatologicznej. Dwadzieścia pięć lat po zabiegu operacyjnym wykryto prawie bezobjawowe liczne ogniska przerzutowe. Chora w wywiadzie wymieniła jedynie nawracające bóle w jamie brzusznej w okresie 1–2 lat przed rozpoznaniem przerzutów. W trakcie zabiegu operacyjnego usunięto część guzów przerzutowych, a następnie poddano pacjentkę chemioterapii, leczeniu ^{90}Y-DOTATATE, a następnie preparatami oktreotydu LAR. W międzyczasie rozpoznano przewlekłą, ciężką niewydolność serca (NYHA IV) w przebiegu złożonej wady zastawki trójdzielnej serca oraz nadciśnienia płucnego. Złożona terapia, typowa dla przewlekłej niewydolności serca razem z długodziałającym analogiem oktreotydu znacznie poprawiły wydolność serca oraz zredukowały objawy zespołu rakowiaka. Jedynym działaniem niepożądanym terapii oktreotydem były hiperbilirubinemia oraz świąd. Długi okres przeżycia jest typowy dla rakowiaka, jednak 30-letnie przeżycie nie było dotychczas opisywane w literaturze. **(Endokrynol Pol 2009; 60 (5): 401–406)**

Słowa kluczowe: *rakowiak, oktreotyd, przewlekła niewydolność serca*

Dr n. med. Marcin Kałużny, Klinika Endokrynologii, Diabetologii i Leczenia Izotopami, AM we Wrocławiu, Pasteura 4, 50–367 Wrocław, e-mail: mkaluzny@poczta.onet.pl

Introduction

Neuroendocrine tumours (NETs) are typically located in the small intestine, predominantly in the ileum. Their incidence is not differentiated between sexes and varies from 2.8 to 8.0 cases per 100 000. Carcinoids are the most common and hormonally active NETs. Their incidence is estimated to be approximately 1.5–2.5 cases per 100 000 of the general population. They are usually slowly growing neoplasms, and even when they exhibit gross local invasion and/or metastases, they are characterized by patients' long survival and good general prognosis. However, metastases appearance and primary tumour diameter above 2 cm worsen the prognosis and limit the 5-year survival rate from 60–70% to 35%. They frequently metastasize to the liver, regional lymph nodes, and occasionally to the bones [1]. The most frequently encountered clinical presentations of carcinoids are intermittent abdominal pain and carcinoid syndrome (diarrhoea, cutaneous flushing, valvular heart disease, bronchoconstriction, myopathy, and an increase in skin pigmentation) when liver metastases occur. It should be pointed out that carcinoid syndrome occurs in less than 10% of patients with carcinoid tumours. Treatment options for non-metastatic small carcinoid tumours are endoscopic mucosal resection, minimally invasive laparoscopic wedge resection, and classic surgery. Surgery is the mainstay and the only potentially curative therapy for carcinoid tumours. Treatment modalities for metastatic carcinoid tumours are orthotopic liver transplant, hepatic artery embolisation, and long-acting somatostatin analogues (octreotide, lanreotide), adjuvant Indium-111, Yttrium-90, or Lutetium-177 octreotide-receptor targeted therapy [2, 3].

Case report and discussion

We report a case of a female patient suffering from a carcinoid tumour with its primary focus in the ileum, diagnosed at the age of 32 years (in 1979) with acute appendicitis symptoms only. The carcinoid was diagnosed postoperatively by a histopathological assessment, but neither Ki67, chromogranin A (CgA), synaptophysin, neurone-specific enolase, nor somatostatin receptor scintigraphy was assessed at that time. The tumour was located in the ileum and infiltrated the appendix, so the distal part of ileum and appendix were removed. After operation all symptoms were withdrawn.

A carcinoid is a hormonally active (serotonin secreting) type of NET located in the small intestine. Most NETs are located in a distal part of the jejunum and ileum (23–38%). These tumours are characterized by worse prognosis due to frequent often lymph nodes and liver metastases [4]. When liver metastases arise, carcinoid syndrome occurs. This is observed in 4-10% of all carcinoid cases [4]. According to current guidelines, immunohistological assessment is an important method for NET diagnosis and prognosis, and for treatment decisions, but in 1979 it was not routine in our country [5, 6]. Patients without liver metastases are noted for longer 10-year survival rates than patients with metastases present at diagnosis [6]. The diameter of the removed tumour was greater than 10 cm and it suggested high risk of metastases present at the time of surgery or arising in the close future, and worse prognosis [7].

The patient's previous medical history was short. When she was 20 years old she had suffered from paroxysmal tachycardia. At the age of 30 she had been administered methimazole due to hyperthyroidism (autoimmune thyroid disease). Remission was achieved after 6 months and L-thyroxine replacement therapy had been started at a stable dose of 50 μg per day. Paroxysmal tachycardia was still present, but in lower frequency. At the age of 55 an abnormal pathway ablation was performed due to Wolff-Parkinson-White syndrome. At that time echocardiography did not reveal any abnormal findings in the heart.

At the age of 57 there was evidence of nearly asymptomatic numerous metastases. The patient was admitted to a gynaecology department. Only intermittent abdominal pain for about 1-2 years prior to diagnosis of metastases was reported. Multiple metastases were located in the parietal peritoneum, omentum, rectum, and sigmoid colon (diameter 2–10 cm), a single tumour in the urinary bladder bottom wall, and multiple bilateral ovarian tumours (5–8 cm in diameter). Hysterectomy, bilateral ovariectomy, omentum, and urinary bladder wall tumour resection were performed. The patient was admitted to the oncology department. The radiologist reported in the first abdominal CT assessment of multiple (above 10) liver hypodense lesions up to 4 cm in diameter (Fig. 1). Carcinoid tumours were also detected by histological assessment in the lymph nodes, but lymphadenopathy was not present. Small bowel carci-

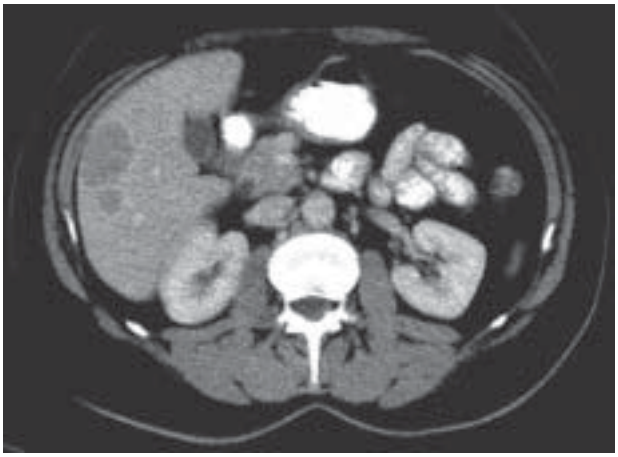

Figure 1. *Carcinoid hepatic metastases (CT scans, January 2004)*
Rycina 1. *Przerzuty rakowiaka do wątroby (badanie CT, styczeń 2004)*

noids are frequently multiple, exhibiting multicentricity in up to 30% of patients [8]. In our patient, some metastases were removed and the total mass of the neoplasm was reduced. Small bowel carcinoids often give metastases to the lymph nodes (39%) and to the liver (31%), as in our patient [7]. Multiple peritoneum and omentum metastases were probably due to carcinoid cell spread during the primary focus resection in 1979. The patient was not presenting typical signs or symptoms, but carcinoid syndrome is generally rare, manifesting in approximately 5–7% of patients. Younger patients are usually more likely to develop carcinoid syndrome, which worsens prognosis [7].

Chemotherapy was performed after partial carcinoid metastases resection. The patient was given 6 times doxorubicin (60 mg/m^2) plus cyclophosphamide every 4 weeks and then 5 times leukovorin (L) plus 5-fluorouracil (5-FU). CT after chemotherapy revealed no changes in comparison to the previous CT scan (stable disease — SD, according to RECIST criteria [9]). Due to sustained abdominal pain, gastrofibroscopy was performed and revealed multiple small mucous tumours in the stomach. Mucous and submucous tissue samples were taken and carcinoid was described in the histopathology assessment. Due to our knowledge, it could be carcinoid metastases or gastric NET type 1 tumour [10]. Three main types of enterochromaffin-like cells (ECL) tumours, could be primary located in the stomach. The most common, type 1, consist of an ECL, well-differentiated cells, often recognized as multiple, multicentric, small stomach tumours. It could be non-functioning or serotonin-, gastrin- or rare ghrelin-producing, and in these cases, "atypical" carcinoid syndrome could occur [11]. The coexistence of two types of NETs (carcinoid and type 1 gastric ECL cell tumour in this case) in one patient is also possible [12]. Hypergastrinaemia is usually observed in type 1 gastric ECL cell tumours, but in our patient hypergastrinaemia and chronic atrophic gastritis was not present, so the gastric tumours were probably carcinoid metastases.

After chemotherapy, as mentioned above, the patient was still nearly asymptomatic (moderate abdominal pain was present only) and tolerated chemotherapy well. The subsequent 6 cycles of L and 5-FU plus intravenous interferon alpha (dose unknown) were administered into the hepatic artery. All cycles of chemotherapy were ineffective. Chemotherapy using 5-FU, streptozotocin, doxorubicin, and cyclophosphamide can be a potent treatment tool, but only in poorly differentiated neuroendocrine tumours with Ki67 above 2% or, even better, above 15% [13]. Proliferation index was not assessed in our patient. The long survival of the patient following primary tumour resection suggests well-differentiated carcinoid, but the lack of carcinoid syndrome symptoms gives rise to poorly differentiated neuroendocrine neoplasm. Chemotherapy was performed based on the oncologist's decision.

At the age of 60, the patient was admitted to the endocrinology department. She reported only mild to moderate diarrhoea and abdominal pain which occurred sporadically. Physical examination revealed obesity (BMI 29.8 kg/m^2) and hypertension (160/100 mm Hg). The hypertension was not complicated. Laboratory assessment showed optimal thyroid replacement (50 μg of L-thyroxine per day). Thyroid ultrasound (US) was normal. Abdominal US revealed multiple hepatic metastases, mild hepatomegaly (13.5 cm), cholecystolithiasis, and celiac trunk region lymphadenopathy, which were confirmed by CT (progression disease — PD, according to RECIST criteria [9]). ECG was normal. The laboratory results are given in Table I.

Serum bone specific alkaline phosphatase, 1,25-dihydroxy vitamin D, CEA, AFP, and other parameters were normal. ^{111}In-Octreoscan somatostatin receptor scintigraphy (SRS) revealed multiple lesions of increased radioactivity in the liver and celiac lymph nodes. Unfortunately, when compared to CT scans and octreotide scintigraphy, not all the metastatic lesions had somatostatin receptor expression. However, the patient was submitted to ^{90}Y-DOTATATE therapy. ^{111}In-Octreoscan SRS before first dose of ^{90}Y-DOTATATE therapy are shown on Figures 2A and 2B. Radionuclide peptide receptor therapy is a novel and potent treatment in patients with NETs and positive ^{111}In-Octreoscan SRS [5–7, 11].

Table I. *Pathological laboratory findings in a patient with carcinoid syndrome before ^{90}Y-DOTATATE therapy*
Tabela I. *Nieprawidłowe wyniki badań laboratoryjnych u chorej z zespołem rakowiaka przed leczeniem ^{90}Y-DOTATATE*

Parameter	Result	Normal range
Fasting glucose [mmol/l]	5.62	3.3–5.5
120′ glucose after oral 75 g glucose tolerance test [mmol/l]	9.38	< 7.7
24 h urine serotonin [μg/24 h]	454.0	50.0–250.0
Chromogranin A (CgA) [nmol/l]	177.8	< 4.0
5-hydroxyindoloacetic acid (5-HIAA) [mg/24 h]	75.0	2.0–9.0

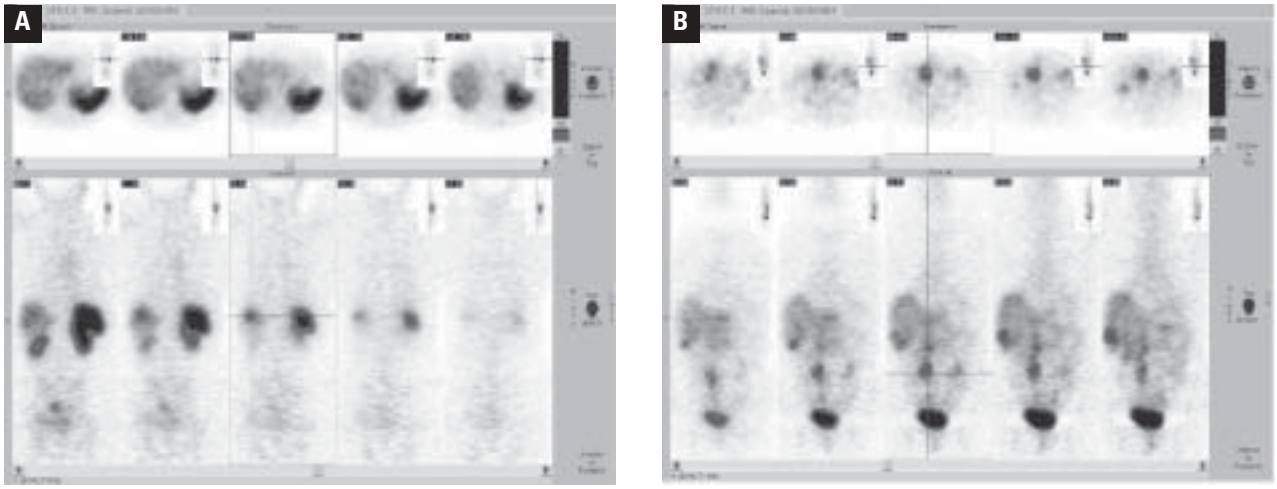

Figure 2. *^{111}In-Octreoscan SRS before first dose ^{90}Y-DOTATATE therapy: carcinoid liver (SVII) metastases (A) and carcinoid peritoneum metastases (B) are visible*

Rycina 2. *Scyntygrafia receptorów somatostatynowych za pomocą ^{111}In-Octreosan przed pierwszą dawką ^{90}Y-DOTATATE: widoczne przerzuty rakowiaka do wątroby (SVII) (A) i otrzewnej (B)*

OPIS PRZYPADKU

Table II. ***Patient's signs and symptoms in March 2008 (according to NCI CTC toxicity scale)***

Tabela II. ***Objawy podmiotowe i przedmiotowe występujące u chorej w marcu 2008 roku (według skali toksyczności NCI CTC)***

Sign or symptom	NCI CTC toxicity scale
Diarrhoea	3
Fatigue	3/4
Dyspnoea	4
Teleangiectasis	1
Abdominal pain	2
Tachycardia	2
Continuous atrial fibrillation	2
Hypertension	2
Cough	3
Nausea	2
Itching	3
Lower limb oedemas	3
Ascites	2
Anxiety	1
Depression syndrome	2
Weight loss	3

Finally, because of cardiac insufficiency (NYHA IV), cardiological therapy was prescribed: perindopril 5 mg/day, bisoprolol 5 mg/day, and aspirin 75 mg/day. From September 2007 to April 2008, 3 cycles of 80 mCi ^{90}Y-DOTATATE were administered. The patient's condition progressively and strongly worsened during the therapy. The following symptoms appeared (Table II). In the laboratory assessment, only mild hyperbilirubinaemia (2.1 mg/dl) and mild anaemia (drop from 13.0 g/dl to 11.5 g/dl) was observed. ECG revealed continuous atrial fibrillation.

Just after the second ^{90}Y-DOTATATE therapy, echocardiography assessment revealed:

— serious combined tricuspid valve defect with predominant regurgitation (Fig. 3 and 4);
— moderate pulmonary valve regurgitation and pulmonary hypertension;
— enlarged right atrium (area 32.8 cm^2, LAD 40 mm) and right ventricle (RVEDD 42 mm) (Fig. 3 and 4);
— mild increased inferior caval vein diameter (25 mm) with decreased respiratory mobility (25/18 mm).

Chronic heart failure in the course of carcinoid heart syndrome was diagnosed and worsened the patient's prognosis [15]. Serotonin, synthesized from the amino acid tryptophan and released into the systemic circulation, causes right-sided valvular heart disease [16]. The chronic heart failure found in our patient was due to right side valvular heart disease. The itching was due to mild hyperbilirubinaemia or more probably due to carcinoid peptides interacting with skin mastocytes. Pruritus is one of the common skin symptoms of metastatic neoplasm, especially serotonin positive (secreting) neuroendocrine tumours [17]. The previously-observed body mass increase was connected to retention of water, muscle, and other soft tissues involution. A new pharmacotherapy was applied: diuretics (furosemide and spironolactone), bisoprolol, ramipril, digoxin, low molecule heparin, gastric proton pump inhibitor, and L-thyroxine. A cardiosurgeon disqualified the patient from valve replacement surgery because of the high risk

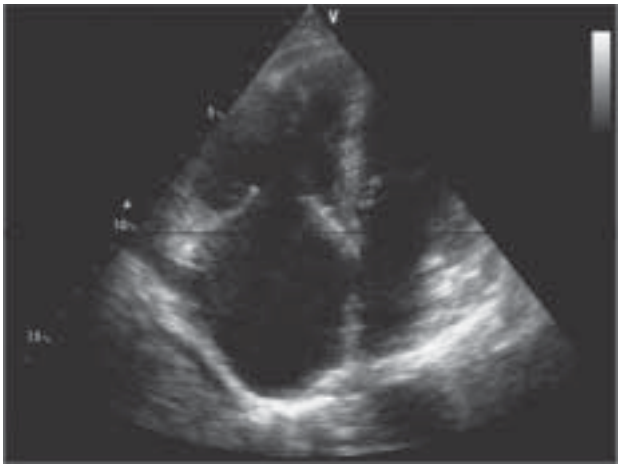

Figure 3. *Tricuspid valve of the patient with carcinoid syndrome: cuspid fibrosis, rigid and shortening. Bicuspid valve is properly open in diastolic. Right ventricle and right atrium dominance according to left ventricle and atrium (apex, 4 caves projection)*

Rycina 3. *Zastawka trójdzielna chorej z zespołem rakowiaka: Zwłóknienie zesztywnienie i skrócenie płatków. Zastawka mitralna: prawidłowa czynność rozkurczowa. Prawe serce (komora i przedsionek) większe niż lewe (projekcja koniuszkowa czterojamowa)*

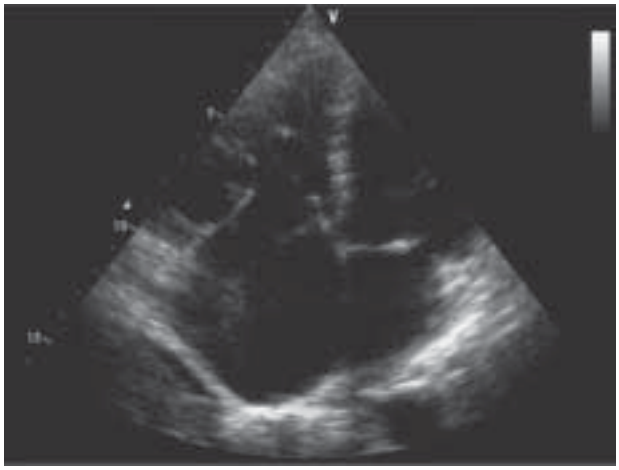

Figure 4. *Systolic phase. Tricuspid valve coaptation loss and proper bicuspid valve coaptation*

Rycina 4. *Faza skurczowa. Niedomykalność zastawki trójdzielnej i prawidłowa czynność zastawki mitralnej*

Table III. *Serum CgA concentrations in a patient with carcinoid syndrome during ^{90}Y-DOTATATE therapy*
Tabela III. *Stężenie CgA w surowicy u chorej z zespołem rakowiaka w trakcie terapii ^{90}Y-DOTATATE*

Parameter	^{90}Y-DOTATATE			
	Before	After 1st cycle	After 2nd cycle	After 3rd cycle
CgA [nmol/l] (normal range < 4.0)	100.2	113.0	143.0	468.0 (60 min. after 100 μg octreotide injection CgA — 391.0)

of metastases progression when using an extracorporeal circulation device, high perioperative death risk, and continuous anticoagulant therapy necessity with high risk of metastases haemorrhage.

After the third cycle of ^{90}Y-DOTATATE there was no clinical improvement (Table III). Therapy was monitored by CgA concentration and abdominal CT scans. CgA is one of the best markers of carcinoid activity and total neoplasm mass [18]. The patient was disqualified from the next ^{90}Y-DOTATATE cycle. Short-acting octreotide analogue test showed good response, so long-acting octreotide (S-LAR) was applied in an increased dose in April 2008. Somatostatin analogues are the first line therapy for symptom remission of neuroendocrine tumours and stabilize hormone production, and may have an anti-proliferative action [3, 5–7, 14, 19].

Since August 2008 the patient has been treated with 30 mg dose of S-LAR. Her condition progressively improved after 6 months of S-LAR therapy. Exercise dyspnoea (NYHA II), increased body weight, retention of water, and mild itching were present. There was no evidence of diarrhoea, cough, lower limb oedemas, or tachycardia. Echocardiography and abdominal CT scans did not change compared to previous exams. Low molecule heparin was changed to ticlopidine due to gastric disturbances with acetylsalicylic acid and difficulties in maintaining therapeutic INR levels during the therapy. The laboratory assessment is shown in Table IV.

In March 2009 there was a marked hormonal improvement — 24 hour urine serotonin was 54.2 μg (reference range 50–250) and CT scans revealed partial remission according to RECIST criteria [9] (Fig. 5). Unfortunately, apart from the improvement, long-term prognosis for patients with carcinoid heart syndrome is poor [20, 21].

We presented this case because the long-term survival is typical for carcinoids, but 30-years survival has not been described in the literature yet.

Table IV. *Pathological laboratory findings in a patient with carcinoid syndrome in January 2009*
Tabela IV. *Nieprawidłowe wyniki badań laboratoryjnych u chorej z zespołem rakowiaka w styczniu 2009*

Parameter	Result	Normal range
24 h urine serotonin [μg/24 h]	342.0	50.0–250.0
Chromogranin A (CgA) [nmol/l]	180.4	< 4.0
5-hydroxyindoloacetic acid (5-HIAA) [mg/24 h]	92.3	2.0–9.0

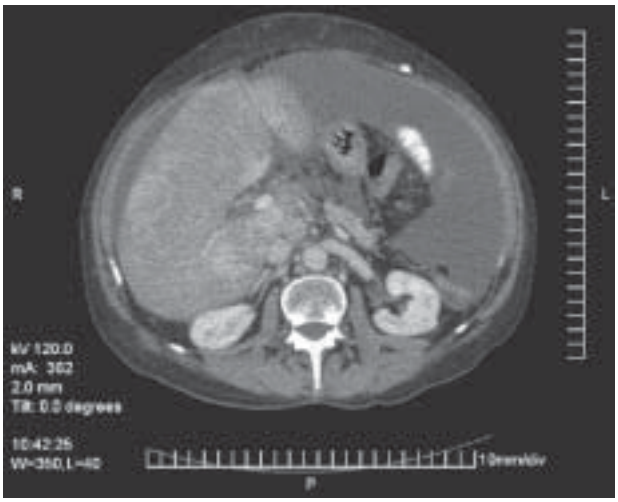

Figure 5. *Carcinoid hepatic metastases (CT scans, March 2009)*
Rycina 5. *Przerzuty rakowiaka do wątroby (badanie CT, marzec 2009)*

References

1. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999; 340: 858–868.
2. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004; 25: 458–511.
3. Ramage JK, Davies AH, Ardill J et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005; 54: 1–16.
4. Godwin JD. Carcinoid tumors. An analysis of 2837 cases. Cancer 1975; 36: 560–569.
5. Bolanowski M, Jarząb B, Handkiewicz-Junak D et al. Guzy neuroendokrynne jelita cienkiego i wyrostka robaczkowego (zasady postępowania rekomendowane przez Polską Sieć Guzów Neuroendokrynnych). Endokrynol Pol 2008; 59: 87–96.
6. Plöckinger U, Rindi G, Arnold R et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. Neuroendocrinology 2004; 80: 394–424.
7. Sippel RS, Chen H. Carcinoid tumors. Surg Oncol Clin N Am 2006; 15: 463–478.
8. Moertel CG, Sauer WG, Dockerty MB et al. Life history of the carcinoid tumor of the small intestine. Cancer 1961; 14: 901–912.
9. Padhani AR, Ollivier L. The RECIST (Response Evaluation Criteria in Solid Tumors) criteria: implications for diagnostic radiologists. Br J Radiol 2001; 74: 983–986.
10. Solcia E, Rindi G, Buffa R et al. Gastric endocrine cells: types, function and growth. Regul Pept. 2000; 93: 31–35.
11. Rindi G, Azzoni C, La Rosa S et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. Gastrenterology 1999; 116: 532–542.
12. Katona TM, Jones TD, Wang M et al. Molecular evidence for independent origin of multifocal neuroendocrine tumors of the enteropancreatic axis. Cancer Res 2006; 66: 4936–4942.
13. Pinchot SN, Holen K, Sippel RS et al. Carcinoid tumors. The Oncologist 2008; 13: 1255–1269.
14. Srirajaskanthan R, Toumpanakis C, Meyer T, et al. Future therapies for management of metastatic gastroenteropancreatic neuroendocrine tumours. Aliment Pharmacol Ther 2009; 9: 921–937.
15. Lim TK, Hayat SA, Gaze D et al. Independent value of echocardiography and N-terminal pro-natriuretic peptide for the prediction of major outcomes in patients with suspected heart failure. Am J Cardiol 2007; 100: 870–875.
16. Robiolio PA, Rigolin VH, Wilson JS et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation 1995; 92: 790–795.
17. Kleyn CE, Lai-Cheong JE, Bell HK. Cutaneous manifestations of internal malignancy: diagnosis and management. Am J Clin Dermatol 2006; 7: 71–84.
18. Nehar D, Lombard-Bohas C, Olivieri S et al. Interest of chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol 2004; 60: 644–652.
19. Welin SV, Janson ET, Sundin A et al. High-dose treatment with a long-acting somatostatin analogue in patients with advanced midgut carcinoid tumours. Eur J Endocrinol 2004; 151: 107–112.
20. Bernheim AM, Connolly HM, Hobday TJ et al. Carcinoid heart disease. Prog Cardiovasc Dis 2007; 49: 439–451.
21. Müller JE, Pellikka PA, Bernheim AM et al. Prognosis of carcinoid heart disease: Analysis of 200 cases over two decades. Circulation 2005; 112: 3320–3327.