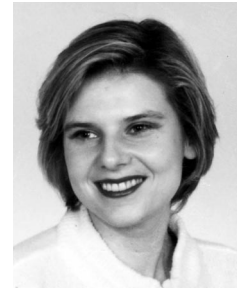


## 58-year-old woman with pancreatic neuroendocrine tumour



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### ABSTRACT

We reported a 58-year-old woman with tumor in the tail and body of pancreas measuring 70 mm in diameter who underwent distal pancreatectomy and splenectomy. Examination of a specimen of the pancreatic mass obtained histopathological features of a *well-differentiated neuroendocrine carcinoma* (WHO 2000 r. NECLM group 2, MIB < 2%). Immunohistochemical staining showed that the tumor cells were positive for chromogranin and synaptophysin. The tumor was radical resected; there were 9 lymph nodes without metastases. The patient was attending routine follow-up 3 years after resection, when ultrasonography detected hepatic tumor with a low echoic area, confirmed as at least 3 lesions in CT. The patient presented with symptoms of general malaise, anorexia, weight loss, diarrhea, and diabetes mellitus. The diagnosis including of the histopathological features resected specimen and symptoms suggested a somatostatinoma. The patient denied the surgery treatment so she was treated with good clinical and biochemical (normalization of chromogranin A) response to octreotide LAR. During follow-up 4 months after, Computer Tomography showed progression. The patient refused suggested chemotherapy streptozotocin combined with doxorubicin. We continued treatment with octreotide LAR, taking into consideration lack of symptoms and stabilization in chromogranin A level, with good result and stabilization in following Computer Tomography.

Somatostatinoma originates from delta cells and is a rare neoplasm, accounting for about 1% of gastroenteropancreatic endocrine neoplasms. About half of somatostatinomas originate in the pancreas, and the remainders originate in other parts of the gastrointestinal tract, mainly in the duodenum. Measurement of the plasma somatostatin concentration is useful for making a diagnosis of somatostatinoma, however is very difficult to perform this examination in our country. Successful treatment with long-acting somatostatin analogues (octreotide LAR) has been reported after progression.

**KEY WORDS:** GEP-NET/NEN – gastroenteropancreatic neuroendocrine tumor/neoplasm, somatostatinoma, octreotide LAR, chromogranin A

**Abbreviations:** NEN – neuroendocrine neoplasm; NET – neuroendocrine tumour; GEP-NEN – gastroenteropancreatic neuroendocrine neoplasm

## CASE DESCRIPTION

A 58-year-old female patient saw a doctor in 2006 for recurrent abdominal pain, taking the form of a painful sensation, flatulence, and steatorrhea, and resulting in a weight loss. At the time, the symptoms had persisted for several months.

Gastroscopy was performed in the patient, revealing a healthy duodenum. In the upper region of the stomach body, on the lesser curvature (in the region of the gastric spur), a slight bulge was observed, of cohesive consistency and a 2.5–3 cm diameter, covered with regular mucous membrane, unattached to the base, with no macroscopic lesions. Focal superficial intestinal metaplasia was observed in the histopathology specimens. The patient's complaints would recur periodically, which is why one year later, a follow-up gastroscopy examination was performed, revealing no abnormalities. As the steatorrhea intensified, the patient was referred for colonoscopy. The large intestine and *ileum terminale* were examined under colonoscopy, confirming no abnormal lesions. Symptomatic treatment was initiated, resulting in no improvement whatsoever.

In 2008, abdominal ultrasound was performed, revealing an enlarged pancreatic tail, with a size of 43–52 mm, and a normoechoic pancreatic parenchyma. Projection of the pancreatic tail revealed an oval hypoechoic 64 × 53 mm lesion, with discrete acoustic enhancement, without any visible vasculature, and most probably representing a pancreatic cyst. Other than that, the ultrasound examination revealed no other abnormalities. The patient remained under observation, subject to symptomatic treatment. Her complaints persisted, and additionally there appeared some carbohydrate metabolism disturbances. 3 months later, a follow-up abdominal ultrasound examination was performed, revealing liver enlargement along the right mid-clavicular line to 181 mm, with no focal lesions, and without signs of vascular modelling; a rounded visceral margin, and signs of steatosis of the hepatic parenchyma. The pancreas was not enlarged in its head and tail regions, and the echogenicity was quite homogenous. Morphology of Wirsung's duct was irregular and up to 1.9 mm in diameter, but with no visible dilatation. Projection of the pancreatic tail revealed a 61 × 53 × 30 mm oval fluid lesion. The first suspected diagnosis was pancreatic pseudocyst. However, even though there was no evident connection with the left kidney structures, and no respiratory mobility, a kidney cyst could not be ruled out (referred for differential diagnosis based on the abdominal CT). Kidneys were found to be typically located, and not enlarged.

Further on, triple-phase abdominal CT was performed, and the findings were as follows: enlarged (191 mm-long right lobe) and hypodense liver (signs of steatosis). Minor calcifications in the

upper part of segment 6, otherwise no focal lesions within the liver. Thin-walled gallbladder, with no concretions. Unenlarged intrahepatic and extrahepatic bile ducts. The pancreatic tail reveals a contrast-enhanced solid lesions, whose size is 48 × 70 × 39 mm. The lesion models the splenic artery, and infiltration of the splenic vein as well as of the adjacent small intestinal loop cannot be excluded. The lesion adjoins the stomach along an extended section, with a partially blurred fatty tissue margin, but it appears that the border between the tumour and the stomach is preserved. The remaining structures surrounding the lesion show no apparent infiltration. The spleen is 125 mm-long, slightly enlarged, with no focal lesions. Accessory spleens: 12 mm and 9 mm. Kidneys and adrenals show no abnormalities. Bilateral accessory renal arteries. Solitary 11 mm-long mesenteric node, and isolated minor mesenteric nodes, and nodes along the aorta. The osseous elements, and the lung fragments visualised under examination demonstrate no lesions suspected of metastases.

## Surgical Treatment

The patient was referred to a general and gastroenterology surgery clinic, where in January 2009, she underwent a peripheral pancreatic resection with splenectomy. During the surgery, the presence of a 5 × 10 cm-large cystic-solid tumour in the pancreatic body and tail was detected, with no signs of infiltrating the neighbouring structures, but closely adjacent to the transverse mesocolon and to the left renal capsule.

## Histopathological Confirmation of NET

Microscopic histopathological assessment confirmed the presence of a *well-differentiated neuroendocrine carcinoma* (NECLM group 2, according to the 2000 WHO classification), with mitotic count > 2/10 HPF. Focal infiltration of pancreatic parenchyma and fatty tissue was reported, and 9 lymph nodes were found, with no metastases. Chromogranin A (+), synaptophysin (+), MIB < 2%; the lesion was totally removed.

## Post-surgical Follow-up

Further on, upon oncological consultation, the patient remained under follow-up, with abdominal ultrasound and CT examinations performed interchangeably every 6 months.

In February 2012, the patient's abdominal complaints reappeared, i.e. flatulence, steatorrhea, weight loss, and rises in the blood glucose level. A follow-up abdominal ultrasound revealed an unenlarged liver, with normoechoic parenchyma. A 7 × 4 mm focal hypoechoic lesion was detected in the central part of the right lobe, extending laterally from the gallbladder, with no flow shown in Doppler examination. Apart from that, there were no

other focal lesions, with the pancreatic body and tail presenting no evident focal lesions for that matter. However, assessment of the patient's stomach was rendered difficult, because of the residual food inside the stomach, and poor visibility.

### Further Diagnostic Procedures

The patient was referred for imaging tests in order to assess the degree of neoplastic advancement. The liver lesions detected in ultrasound required further diagnostics.

The following tests were applied for the purpose: computed tomography (CT) with intravenous contrast (arterial phase assessment is also important), and scintigraphy with radiolabelled somatostatin analogues.

**Abdominal and pelvic CT with intravenous contrast:** liver parenchyma revealed at least three poorly defined and slightly hypervascular focal lesions, sized 12 mm, 7 mm and 7 mm, located in segment 7. The lesions were not visible on venous phase. The image bore suspicion of metastatic lesions, and visualised a post-splenectomy and distal pancreatectomy condition. The remaining organs within the abdominal cavity and small pelvis, as well as the visualised basal pulmonary segments revealed no abnormalities.

**Scintigraphy with radiolabelled somatostatin analogues:** SPECT/CT somatostatin receptor scintigraphy (SRS), centred on abdominal and thoracic cavities ( $^{99m}\text{Tc}$ HYNIC TOC, 800 MBq), demonstrated small focal lesions within the liver, with abnormal and intensive accumulation of the radiolabel. There were over 10 such lesions visible in the right hepatic lobe. Accumulation intensity – Krenning 4. There were no other focal lesions showing abnormal accumulation of the label.

Later on, the patient was referred to the Maria Skłodowska-Curie Institute of Oncology at ul. Wawelska for consultation and further treatment.

The patient's concomitant diseases: arterial hypertension and diabetes. Medications taken: ramipril 5 mg, metformin 1500 mg/24 h, pancreatin 25 000 U 3 times daily, omeprazole 40 mg.

Family history: mother – uterine body cancer, father – HCC.

Complaints: poorly controlled diabetes, with failed attempts at starting the patient on insulin due to dose selection problems (episodes of hypoglycaemia), steatorrhea, regardless of the diet and the pancreatin ingested, stomach-ache, weight loss.

### Physical Examination

Good general condition. Regular cardiac activity 78/min, without accidental cardiac murmurs, arterial pressure 140/75 mmHg, without orthostatic hypotension. Normal vesicular sounds over the lung fields under auscultation. Soft abdomen, tender under palpation, with no pathological growths or resistance. Liver – not

enlarged. Intensified, well audible peristalsis. With no peripheral oedema.

### Biochemical Diagnostics

**Chromogranin A (CgA)** is the most frequently applied non-specific indicator for neuroendocrine tumours, as it is a protein which is produced, stored, and released by neuroendocrine cells, and then secreted into the bloodstream together with other hormones by means of exocytosis. CgA concentration is significantly elevated in most NETs, while in-range results do not exclude the possibility of NEN. On the other hand, concentration levels that go beyond normal limits do not always stem from the presence of NEN, and are not enough for diagnosis, which is why the results need to be interpreted with due caution. Specificity of the assay is higher in more advanced conditions, i.e. in NEN with liver metastases.

Baseline concentration of chromogranin A in the patient in question, following withdrawal of proton pump inhibitors for 3 weeks, was 298 ng/ml (with the normal range of up to 94 ng/ml).

The patient's case was discussed at a meeting of a multidisciplinary medical team. It was decided that the patient be referred for consultation with an oncological surgeon in order to consider right hemihepatectomy. Additionally, a suggestion was made that perhaps the neoplasm in question was a very rare functioning neuroendocrine pancreatic tumour referred to as the *somatostatinoma*, and the decision was taken to make an attempt at starting the patient on cold somatostatin analogues (LAR octreotide). *Somatostatinoma*-related symptoms are caused by the suppressive impact of somatostatin on the endocrine function of pancreas and other organs (leading to inhibited secretion of insulin, glucagon, cholecystokinin, gastrin, and other hormones), and on the exocrine pancreatic function. Classical symptoms of *somatostatinoma* involve diabetes (or other carbohydrate metabolism disorders), weight loss, and steatorrhea. Somatostatin concentration characteristic of *somatostatinoma* exceeds 1000 pg/ml (with the normal limit of 100 pg/ml). On the other hand, normal concentration of somatostatin does not rule out the diagnosis of *somatostatinoma*. There are few possibilities of determining somatostatin concentration in clinical practice, which is why the assay was not performed in the patient.

Having been informed on the possible future management of the disease, the patient refused to consult with a surgeon as to the potential hemihepatectomy aimed at the resection of metastatic lesions.

### Further Management

The patient was in a relatively good general condition, but reporting steatorrhea up to 14 times a day, paroxysmal stomach-ache,

and weight loss. She was qualified for treatment with a long-acting somatostatin analogue, LAR octreotide, because of its suppressive impact on hormonal secretion, and probable anti-proliferative effect, stabilizing and delaying disease progression. In the PROMID study (randomized phase III trial) LAR octreotide dosed at 30 mg has been shown to significantly extend time to progression in patients with advanced neuroendocrine neoplasms. The trial concerned neoplasms originating from the middle section of the archenteron or neoplasms of unknown primary foci, but there are also other findings involving another somatostatin analogue, lanreotide, which has demonstrated anti-proliferative effect in non-functioning neuroendocrine tumours, including the pancreatic ones.

Before the initiation of treatment, it was suggested that the patient undergo cholecystectomy, but the patient refused to give her consent to the procedure. The rationale behind the proposal was that cholelithiasis develops in 20–50% of the patients treated with cold analogues, with possible further complications.

Four months into the treatment, chromogranin A dropped to 41.2 ng/ml, abdominal pain and steatorrhea receded, blood glucose was better controlled, and the patient gained some weight. The treatment was continued, with follow-up CT and receptor scintigraphy performed 4 months into the treatment. Concentration of chromogranin A stayed within the normal range, and the patient remained asymptomatic.

**Triple-phase abdominal and pelvic CT with intravenous contrast:** progression was observed as compared to the baseline CT, with new foci of hypervascular metastases in the liver parenchyma, and the previously detected lesions grew bigger. The examination revealed 16 focal lesions at the time, visualising a condition following pancreatic tail resection and splenectomy. Pancreatic head and body revealed no focal lesions or signs of other abnormalities. Intrahepatic bile ducts and common bile duct were unenlarged. Cholecyst was not enlarged, thin-walled, and with no concretions. Kidneys and adrenals did not show any significant lesions. There were no enlarged lymph nodes. The parts of lungs and the osseous structures visualised under the CT examination revealed no lesions that would suggest metastases.

The patient's case was discussed at a case management conference, and it was decided to introduce mTOR inhibitor treatment, administering everolimus dosed at 10 mg, based on the results of the RADIANT-3 phase III trial, which confirmed the efficacy of everolimus in the treatment of advanced pancreatic neuroendocrine tumours. The study involved 410 patients diagnosed with an advanced pancreatic NET, in whose case disease progression had been radiologically confirmed over the preceding 12 months. The study demonstrated a statistically significant improvement

as regards progression free survival (PFS), which was the primary endpoint of the trial. PFS was 11 months in the group of patients on everolimus, and 4.6 months in the placebo arm. The treatment was well-tolerated by the patients, which is why an application was filed with the National Health Fund (NFZ), requesting approval of non-standard therapy. The application was rejected, though.

Hence, chemotherapy was offered to the patient. In pancreatic neuroendocrine tumours, the applied regimens are multi-drug regimens based on streptozotocin (STZ). The efficacy of such regimes has been demonstrated in a phase III trial designed by Moertel and collaborators. 69 study participants with neuroendocrine pancreatic tumours, subject to the chemotherapy schemes involving STZ + DOX vs STZ + 5-FU, demonstrated response rates (RR) of 69% vs 45% respectively, with mean RR duration of 18 vs 14 months, and mean overall survival (OS) of 26 vs 18 months. Consecutive studies have indicated response rates of around 36–55%, following STZ + DOX ± 5-FU, with RR duration of 11–22 months, and mean overall survival of slightly over 20 months.

Streptozotocin is still considered standard treatment in pancreatic NENs, even though there are no randomized trials comparing the STZ-based regimens with other therapies. Moreover, it is worth mentioning that STZ is not registered in Poland, and it can only be administered as a result of direct import and approval of non-standard chemotherapy. Having been informed on the possible adverse events and side effects pertaining to the treatment, the patient failed to give her consent to it. Therefore, it was decided that the patient continue the symptomatic treatment, as there were disease symptoms, and chromogranin A concentration remained normal (36.6 ng/ml). In case of disease progression, PRRT isotope treatment remains to be considered.

The patient has now been treated with LAR octreotide for a year, manifesting very good clinical tolerance. Abdominal pain and steatorrhea have receded, blood glucose is better controlled, and there has been some weight gain. The consecutive abdominal and pelvic CT examinations have confirmed stable disease. The last examination reported a comparable number of metastatic lesions as the previous tests, with a tendency for a nearly 7% decrease in the number of the lesions. Follow-up SPECT/CT scintigraphy, performed in order to assess the expression of the SST2 receptor in the lesions detected, making use of the radiolabelled somatostatin analogues, and centred on the abdominal and thoracic cavities ( $^{99m}\text{Tc}$ HYNIC TOC, 800 MBq), revealed more numerous focal lesions within the liver, showing abnormal intense accumulation of the radiolabel, as compared to the baseline test. Accumulation intensity – Krenning 4. No other focal lesions, manifest-

ing abnormal accumulation of the label, were observed under the examination. Concentration of chromogranin A remains within norm (53.8 ng/ml).

## DISCUSSION

Pancreatic NET incidence is 4–12 cases per million a year, which constitutes only 2% to 10% of all pancreatic cancers. Most of them are highly- and medium-differentiated G1 and G2 tumours, according to the 2010 WHO classification, with the dominant position of *insulinoma* and non-functional pancreatic tumours. The incidence is similar in female and male patients, and the neoplasms manifest high diversity as for their degree of malignancy and clinical course. Hence, they require a variety of imaging methods, both anatomical and functional ones. The treatment of choice is surgery. In every case of a neuroendocrine tumour with liver metastases, it is recommended to perform receptor scintigraphy. The examination makes it possible to assess neoplastic advancement, and facilitates the decision-taking process as regards further therapeutic options. Presence of somatostatin receptors within the tumour and its metastases is characteristic of highly- and medium-differentiated NEN/NET, and enables the use of somatostatin analogues (if the tumour is hormonally functional) or the initiation of radioisotope therapy. Somatostatin analogues inhibit secretion and proliferation, influencing somatostatin receptors, and exhibiting the highest affinity to the receptor subtypes of SST 2, 3 and 5. Based on the patient's clinical symptoms, doctors suspected a very

rare pancreatic neuroendocrine neoplasm – *somatostatinoma*.

Incidence of *somatostatinoma* (estimated as 1 : 40 000 000) is comparable in both sexes, and the mean age at diagnosis is 50. The neoplasm is usually located in the pancreas (ca. 60% of the cases), duodenum, ampulla of Vater, and the small intestine. Upon diagnosis, around 75% of the tumours have already disseminated. The size of the primary focus is usually beyond 5 cm. *Somatostatinoma*-related symptoms are a result of the suppressive effect of somatostatin on the endocrine function of the pancreas and other organs, as well as on the exocrine pancreatic function. Some of the classical symptoms, stemming from the above mentioned effect of somatostatin, involve diabetes (or other carbohydrate metabolism disorders), cholelithiasis, and steatorrhea. Frequently, there are also non-specific symptoms, related to the tumour mass, such as abdominal pain, dyspepsia, eructation, and weight loss. Clinical diagnosis can be confirmed by means of determining serum somatostatin concentration. Concentrations characteristic of *somatostatinoma* are believed to be the ones beyond 1000 pg/ml (with the normal range of up to 100 pg/ml). However, normal concentration of serum somatostatinoma does not rule out the diagnosis of *somatostatinoma*. Moreover, there are few possibilities of determining somatostatin concentration in clinical practice. Additionally, the neoplasm can also secrete other hormones.

When treating pancreatic neuroendocrine neoplasms, there are several therapeutic options, but with no established management algorithm. Presently, research is under way as regards the standards of sequential treatment.

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