Combined octreotide and peptide receptor radionuclide therapy (^{90}Y-DOTA-TATE) in case of malignant insulinoma

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Abstract

BACKGROUND: Insulinomas are the most common functioning neuroendocrine tumours of the pancreas. Hypoglycemia due to excessive production of insulin is a main feature of this disease. Usually these neoplasms are benign and single with surgical excision as a treatment of choice. About 10% are malignant with tendency to form metastases especially to the liver then therapy requires various medical technics.
CASE REPORT: 43 years old female with reccurent syncopies in course of hypoglycemia was admitted to the hospital to be diagnosed. Having suspected pathology within the pancreas the abdominal MRI was performed. It showed presence of numerous metastatic changes in the liver with no any other deviations in the abdomen including pancreas. Subsequent 18FDG PET-CT revealed metastases to the regional lymph nodes and the liver and suggested the presence of a primary lesion in the tail of the pancreas which was confirmed in EUS. Surgical excision of the tail of the pancreas was done. Pathological result: pancreatic neuroendocrine well differetiated cancer. Due to the recurrence of hypoglycemia patient was admitted to Department of Endocrinology where somatostatin analogue scintigraphy showed the presence of tracer accumulation foci in the liver. Combined long-acting somatostatin analogue (octreotide) and peptide radionuclide receptor (^{90}Y-DOTA-TATE) therapy were introduced. Stable blood glucose levels with no tendency to hypoglycemia and partial regression (PR) of liver lesions according to RECIST citeria were observed in course of the treatment.

CASE REPORT

INTRODUCTION

Functioning pancreatic tumors represent about 30% of all pancreatic neuroendocrine tumors, among which the most common are insulinomas. The incidence of pancreatic insulinomas is estimated at 1–3 cases per million population per year (de Herder *et al.* 2011).The median age of patients at diagnosis is about 47 years, with a female dominance (female:male = 3:2).Usually these neoplasms are benign and single, but about 10% are malignant with a tendency to form metastases, especially to the liver and 10% are multiple tumors (Vaidakis *et al.* 2010). Insulinomas are located within the pancreas and their location is equally divided over the tail, body and head portions.

Classic symptoms that require further investigation in the direction of excessive production of insulin is described in 1935 by Whipple and Frantz triad, which consists of: 1) neurological symptoms of hypoglycemia, 2) glucose level below 50 mg/dl, 3) rapid relief of symptoms after glucose administration (Whipple *et al.* 1935). Surgery is a treatment of choice for insulinoma which gives high success rate in the case of benign tumors. A significant therapeutic challenge are cases of metastatic disease, which requires various medical techniques.

CASE REPORT

43 years old female (54 kg weight, 162 cm height, BMI 21 kg/m^2) was admitted to hospital due to reccurent syncopies in course of hypoglycemia (glucose level: 35 mg%). According to patient and family report several syncopies had been repeated from 2 months, lack of hypoglycaemic therapy. She suffered from iron deficiency anaemia and gastroesophageal reflux disease. Medicaments in use: iron supplementation and proton pump inhibitors (pantoprazol).

On admission, general condition good, RR 130/70, with no deviations in the physical examination.

In laboratory studies low levels of blood glucose (45 mg%) with normal insulin level and elevated C-peptide, except that no any other deviations, negative blood tumor markers.

Having suspected pathology within the pancreas the abdominal MRI was performed. Scans demonstrated the presence of numerous metastatic changes in the liver (more than 10 oval-shaped foci in both lobes of the liver, the largest with a diameter of 4.5 cm in the right lobe segment VI, in the left lobe diameter of 3.5 cm in segment IVB, the other abdominal organs including the pancreas morphologically normal, without focal lesions or neoplastic infiltrations, and no pathological contrast reinforcements which might indicate the proliferative process.

Having tried to expand the diagnosis of primary lesion chest X-ray, gastroscopy, colonoscopy, ultrasound of the thyroid gland, gynecological consultation, mammography, echocardiography were done, which showed no significant changes.

Biopsy of the tumor in the liver under CT control was done, but it did not give a clear pathological result.

Eventually PET/CT with ^{18}FDG (fluorodeoxyglucose) was performed and the image suggested the presence of a primary lesion in the tail of the pancreas with metastases to the regional lymph nodes and the liver. Subsequent endoscopic ultrasound (EUS) cofirmed pathological lesion within pancreatic tail.

The patient was transferred to the Department of Surgery, where the laparotomy was decided to be done. During the operation pancreatic tail was removed and splenectomy was done.

Due to the numerous metastases in the liver widening surgery was abandoned.

Material was sent to Department of Pathology for the examination.

The histopathological result – macroscopically: tumor size 1.5×3.4×2 cm within the pancreatic tail, which reached into the cavity of the spleen, but did not infiltrate it.

In adipose tissue, numerous lymph nodes from 0.7 cm to 1.8 cm

Microscopic examination: a preliminary determination of the neuroendocrine tumor.

Additional immunohistochemical study was performed to confirm the diagnosis.

Final diagnosis: pancreatic neuroendocrine well differetiated cancer G2, according to WHO classification: group 2 (chromogranin +, synaptophysin +), Ki67 proliferative index of 3%.

During patient's stay in the surgical ward, no decreases of glucose levels in the blood were observed.

One month after surgery the patient re-admitted to hospital because of worsening of logical contact, fainting in the course of hypoglycemia. Patient without any logical contact, confused with cold sweaty skin. CT of the head was performed to exclude a possible intracranial bleeding, which revealed no pathology in the CNS. Blood glucose level was 41 mg%. Intravenous glucose infusion was administered rapidly.

The patient was transffered to the Department of Endocrinology for the further treatment. Decreases in blood glucose (45 mg%) with overranged values of insulin and C-peptide (fasting insulin 24 µU/ml (normal 3–17), C-peptide 45 ng/ml (normal 0.01–40) were observed. Chromogranin A, non-specific marker for neuroendocrine tumors bacame within a normal range (50 ng/ml, norm 19–100). To exclude MEN 1 syndrome (multiple endocrine neoplasia) PTH, calcium, phosphorus and pituitary hormones were checked. No deviations were observed. During hospitalization receptor scintigraphy combined with SPECT-CT was performed with the use of somatostatin analogues (^{99m}Tc EDDA/HYNIC-TOC), which revealed the presence of tracer accumulation foci in the liver (Figure 1). Apart from lesions in the liver no any other pathologi-

cal tracer accumulation has been demonstrated within the body. The study confirmed the presence of somatostatin receptors in metastatic foci. Pre-treatment with short acting somatostatin analogues was performed with good tolerance, no glucose level falls below normal range during hospitalization. Long-acting somatostatin analogues treatment (Sandostatin LAR 30 mg) in monthly injections was administered – during several months of observation blood glucose levels stayed just above the lower range with no tendency to hypoglycemia, no signs of hypoglycemia and with normal levels of insulin, C-peptide, chromogranin A.

Due to the numerous changes in the liver with positive expression of somatostatin receptors combined treatment including peptide radionuclide receptor therapy (^{90}Y-DOTA-TATE) and further somatostatin analogue therapy was introduced.

In posttherapeutic scintigraphy after administration of 100 mCi ^{90}Y-DOTA-TATE i.v radiopharmaceutical accumulation was observed in focal changes in the liver (Figure 2). After three courses of treatment with peptide radionuclide receptor therapy given every three months and 12 months of treatment with somatostatin analogues (Sandostatin LAR 30 mg im every 4 weeks) partial regression (PR) of liver lesions according to RECIST citeria was observed, with stable blood glucose levels and without any side effects of the therapy (correct values of creatinine, eGFR, blood counts) and patient well-being. Till now patient has maintained a constant body weight (54 kg) without any particular diet. It was decided to continue treatment with a combined injections of somatostatin analogues and isotope therapy.

DISCUSSION

Pancreatic neuroendocrine tumors are the most common tumors derived from the diffuse neuroendocrine system and represent approximately 1–2% of all tumors originating from the pancreas (Yalcin 2011). The incidence of pancreatic neuroendocrine tumors has grown in the past 16 years 2–3 times, while the incidence of adenocarcinomas of the pancreas has remained unchanged over the past decades (Yao *et al.* 2008; Halfdanarson *et al.* 2008). Although most of neuroendocrine pancreatic tumors are hormonally inactive some

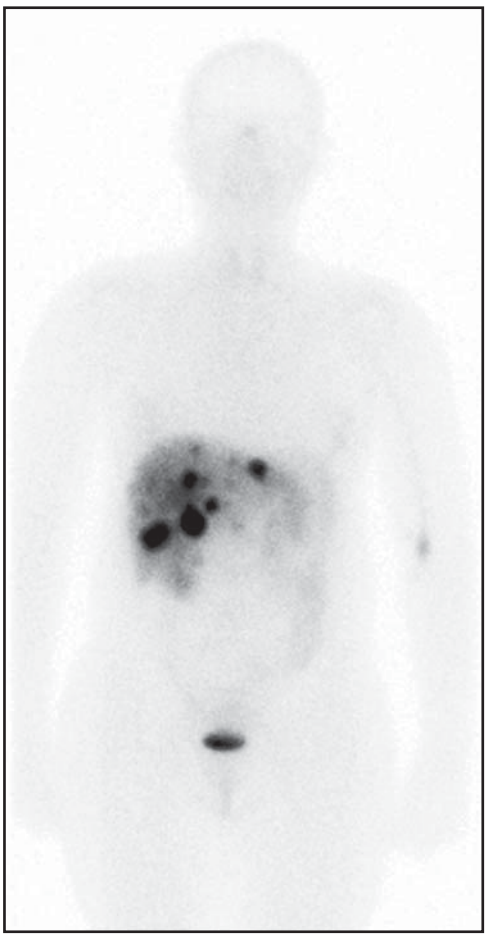

Fig. 1. ^{99m}Tc EDDA/HYNIC-TOC scintigraphy: presence of tracer accumulation foci in the liver (metastases).

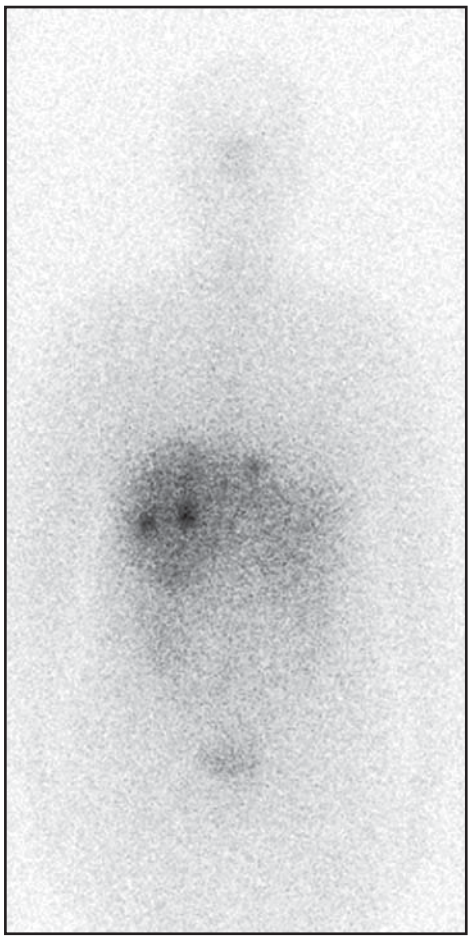

Fig. 2. Posttherapeutic scintigraphy after administration of 100 mCi ^{90}Y-DOTA-TATE.

of them secrete hormones causing syndromes associated with their excess. Among those functioning tumors insulinomas are the most common neoplasms, which constitute up to 70–80% of that group (Halfdanarson *et al.* 2008). Although the vast majority of these tumors are solitary, sporadic tumors, a part of them (10%) may be associated with multiple endocrine neoplasia type 1 (MEN type 1), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1) or nodular sclerosis (TSC) . In these cases, the malignancy of tumors is much higher and they tend to appear at a much younger age.

Survival rate depends on the type of tumor, its differentiation, disease stage, surgical treatment options. The overall 5-year survival rate of patients referred to the recent studies ranges from 42% to 65% (Ekeblad *et al.* 2008; Lepage *et al.* 2004; House *et al.* 2006).

Clinical symptoms of insulinoma are the consequence of the symptoms of hypoglycemia, and might be divided into those related to neuroglycopenia (headache, dizziness, tinnitus, blurred or double vision, amnesia, confusion and even unconsciousness) and those associated with the adrenergic reaction of the body (sweating, palpitations, hunger, nervousness). Insulinoma should be included in the differential diagnosis in the presence of these symptoms, as well as in the case of fasting hypoglycaemia in potentially healthy-looking people. Clinical manifestation may mimic neurological and psychiatric diseases as occurred in our case. The diagnosis might be made by demonstrating nonsuppressed plasma insulin, proinsulin and/or C-peptide levels in the presence of hypoglycemia. Gold standard for diagnosis of insulinoma is a 72-hour fast. No symptoms during the test may exclude insulinoma with almost 100% certainty. Other diagnostic techniques, although they are rarely performed are secretine test or C-peptide inhibition test after administration of exogenous insulin.

Differential diagnosis

During differential diagnosis of hypoglycemia drugs should be considered at first, of which insulin is the most common cause in hospitalized patients (Seltzer 1989). Among the non-antidiabetic drugs which may cause hypoglycemia quinolones, pentamidine, quinine, ACEI, beta-blockers (Murad *et al.* 2009), as well as painkillers (Taugourdeau *et al.* 2011) have been reported.

Among other causes of hypoglycemia renal/liver failure, sepsis, as well as non-insulinoma hypoglycemia pancreatogenous syndrome (NIPHS), insulin factitial hypoglycemia, strenuous exercise, and ketotic hypoglycemia should be considered (Vaidakis *et al.* 2010). Hormonal disorders like adrenal inssuficiency, hypopituitarism, hypothyroidism should also be excluded. Additional causes include alcohol poisoning and congenital disorders of carbohydrates metabolism.

However, cases of insulinomas are the most common causes of hypoglycemia.

Techniques for tumor localization

Detection of insulinoma is usually a challenge, because these tumors often have a diameter of less than 2 cm. Among radiological technics endosonography (EUS) is considered to have the highest sensitivity reaching 63–95%, sensitivity of CT and MRI oscillates around 40% (Hagel *et al.* 2011).

Currently the most useful method of nuclear medicine for imaging of neuroendocrine tumors is a PET with use of 68-galium labeled somatostatin analogues, which has a higher value than scintigraphy with SPECT octreoscan, including CT scanning or MRI (Czepczynski *et al.* 2010).

Positron emission tomography (PET) with use of 18FDG (fluorodeoxyglucose) does not give, in most cases, satisfactory results because of the low-proliferative potential of cancer cells. Whereas FDG-PET has a variable sensitivity overall, there is emerging evidence that presence of increased glucose metabolism in tumor highlights an increased propensity for invasion and metastasis and overall poorer prognosis (Tan *et al.* 2011).

There have been report about completely new marker in PET imaging – GLP-1 (glucagon like peptide type 1) analogue, EM3106B, labeled with (18)F , which receptors are expressed with high density and incidence in insulinoma tumors (18F-FBEM-EM3106B) (Gao *et al.* 2011).

Somatostatin receptor scintigraphy is a commonly used technic of visualisation of neuroendocrine tumors which is based on their specific feature: expression of somatostatin receptors on the surface of neoplasms cells. The problem is that the vast majority of insulinomas are benign tumors, where the expression of somatostatin receptors is observed only in 50% of cases. In those situations scintigraphy might give false negative results. Better results are obtained by use of somatostatin analogue receptor scintigraphy in malignant tumors, because the expression of somatostatin receptors in those cases is generally higher (Virgolini *et al.* 2005). In the absence of visualization of the tumor with a high probability of its existence explorative laparotomy with manual examination of pancreas or intraoperative ultrasonography is advocated. The sensitivity of this method of detection is highest and reaches 97% (Falconi *et al.* 2002).

Treatment

Surgery is a first line treatment for benign insulinoma and has an extremaly high success rate. However, even in the metastatic disease, resection of primary focus should be considered. It might result with reducing the symptoms associated with the disease and may affect the length of survival (Hodul *et al.* 2008).

Diazoxide is a drug used for conservative treatment, administered orally can inhibit the secretion of insulin and normalize blood glucose levels due to inhibition of

potassium channels. The effectiveness of this treatment is estimated at approximately 50% (Grant 2005).

Side effects are the common problem during this kind of treatment (nausea, vomiting, tachycardia, thrombocytopenia, neutropenia) and no effect on tumor size. Intravenously given diazoxide lowers blood pressure by relaxing smooth muscles.

The basis for the use of **somatostatin analogues** is high expression of somatostatin receptors on the surface of more than 80% of neuroendocrine tumors according to autoradiographic and scintigraphic studies(Reubi *et al.* 1990, Krenning *et al.* 1993).

Somatostatin analogues (SA) are the treatment of choice in functioning endocrine tumors to control clinical symptoms by inhibiting hormones or biologically active substances. They also show antiproliferative potential. Natural somatostatin has an affinity to all five somatostatin receptors, while the synthetic analogues have an affinity to the several receptors, especially 2 (SSTR2), also 5 (SSTR5) and slightly to the receptor 3 (SSTR3). Benign forms of insulinoma typically do not express SSTR2 on their surface (Lamberts *et al.* 1996), as a contrast malignant insulinomas may show a high percentage of SSTR2 (Eriksson 2011). Treatment with comercially available SA can diversely affect blood glucose concentration. In case of lack somatostatin receptors on neoplasm surface they may paradoxically decrease blood glucose due to inhibition of hypoglycemia contrregulating hormones (growth hormone, glucagon) (Oberg *et al.* 2009). The use of somatostatin analogues is justified only in cases when expression of somatostatin receptors was confirmed in vivo (somatostatin receptor scintigraphy) or in vitro (immunochemistry) on biopsied/removed tissue specimen.

Peptide receptor radionuclide therapy is a promising form of therapy used in cases of advanced not eligible for radical surgical removal malignant tumors. The most common used substances in this case are yttrium (^{90}Y) or lutetium (^{177}Lu) labeled somatostatin analogues, which are the sources of beta radiation. A prerequisite for this treatment, as mentioned above, is to demonstrate a strong expression of somatostatin receptors in tumor foci. All somatostatin receptor radionuclide therapy is based on the principle of the binding of a radiolabeled ligand to the somatostatin receptor. Somatostatin analogue binded to SSTR causes a characteristic inhibitory effect of somatostatin and coupled with radioactive compound exhibits destructive effect by local short but high energetic beta radiation. Kwekkeboom et al. describes the effectiveness of therapy with radionuclides in the group of five metastatic insulinomas. According to RECIST criteria PR (partial response) received 3 of 5 patients, 1 had SD (stable disease) and 1 had PD (progressive disease) (Kwekkeboom *et al.* 2008). The effectiveness of PPRT therapy of malignant insulinoma with hypoglycaemia is also descibed by other authors (Ong *et al.* 2010; van Schaik *et al.* 2011).

There is growing interest in the local treatment with selective internal radiation (SIRT) using yttrium-90. Due to the local administration of radiation doses up to 1000 Gy can be administered to the tumor, causing its destruction. This is a quite new method, the preliminary data shows stabilization of cancer about 65% in the one year observation (Mc Stay *et al.* 2005) .

Chemotherapy: In the case of aggressive neuroendocrine metastatic pancreatic tumors with high miotic potential chemotherapy is applied: streptozotocin in combination with 5-fluorouracil (5-FU) or doxorubicin. Response to this treatment varies and ranges from 10–70% depending on tumor type including insulinoma (Moertel *et al.* 1980; Cheng *et al.* 1999; Eriksson *et al. 2009)*.

There are reports of efficacy of chemotherapy with capecitabine and temozolomide as first-line therapy in patients with pancreatic neuroendocrine tumors (including insulinoma) acquiring 70% of objective response to treatment, with a median progression-free survival 18 months and 92% 2-year of survival (Strosberg *et al.* 2011).

Future perspectives: Two new drugs have been recently approved by the FDA for treatment of unresectable pancreatic neuroendocrine tumors (PNETs): everolimus and sunitinib. Everolimus an oral inhibitor of the mammalian target of rapamycin (mTOR) showed promising results in two phase 2 studies of patients with PNETs. mTOR is a serine-threonin kinase that stimulates cell growth, proliferation, and angiogenesis. Sunitynib is an oral multitargeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF). There are reports showing effectiveness of insulinoma treatment with normalization of blood glucose during everolimus therapy (Kulke *et al.* 2009, Fiebriech *et al.* 2011). Those brand new agents gives promising results in treatment of pancreatic neuroendocrine tumors but need further studies especially according to insulinoma.

CONCLUSION

Insulinoma, compared to other neoplasms, is a very rare unit giving various symptoms due to hypoglycaemia. Having excluded inapropriate use of hypoglycemic drugs, the most common cause of hypoglycemia, insulinoma should be included into the differential diagnosis. Tumor localisation after confirmation by laboratory tests and subsequent total surgical excission gives extremaly high percentage of recovery. Having deal with malignant metastatic insulinoma further proceedings needs to be considered individually in order to patient condition, associated symptoms, neoplasm agressivness or somatostatin receptor expression. New perspectives of visualisation and treatment are encouraging but need further studies. Appropriate developed strategy might give promising results in tumor response and patient well being.

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