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Insulinoma in a patient with MEN 1 syndrome — 9-year follow-up: case report

Insulinoma u pacjenta z zespołem MEN 1 — 9-letnia obserwacja: opis przypadku klinicznego

Marcin G. Dębski, Anna Makowska, Ewa Bar-Andziak

Department of Internal Medicine and Endocrinology, Medical University, Warsaw

Abstract

Introduction: Multiple endocrine neoplasia type 1 (MEN 1) is a rare autosomal dominant inherited endocrine disease characterized by pancreatic, parathyroid, and anterior pituitary tumours. Hypercalcaemia due to parathyroid tumours is usually the first manifestation of MEN 1. Pancreatic islet tumours occur less frequently, among them gastrinomas and insulinomas are the most prevalent. Prolactinomas are a relatively common pituitary presentation of the syndrome. The gene causing MEN 1 is localized in chromosome 11q13 and encodes a protein named menin, which interacts with various proteins involved in transcriptional regulation, cell division, and DNA repair. Various mutations in the menin gene have been described, but so far no strong correlation between genotype and phenotype has been found.
Case report: We report a case of a 31-year-old man, a lawyer, who was diagnosed with MEN 1 syndrome in 1999 at the age of 21 when he was operated because of prolactinoma and hyperparathyroidism. In 2000 insulinoma was suspected and eventually multifocal lesions in the pancreas were revealed. However, the patient did not agree to be operated on. Since then he has been followed up and has been treated with diazoxid. We observed gradual progression of the disease, but the patient remains in relatively good condition.
Conclusions: Careful screening for MEN 1 is important in young patients with pituitary tumours. Regular follow up is crucial even after surgical treatment. The presented patient developed gradual enlargement of insulinomas and reoccurrence of hyperparathyroidism as well. **(Pol J Endocrinol 2010; 61 (2): 212–216)**

Key words: *MEN 1 syndrome, insulinoma, menin, mutation*

Streszczenie

Wstęp: Zespół MEN 1 jest rzadkim schorzeniem dziedziczonym w sposób autonomiczny dominujący charakteryzujący się współwystępowaniem guzów trzustki, przytarczyc i przysadki. Hyperkalcemia spowodowana guzami przytarczyc jest zwykle pierwszą manifestacją tego zespołu. Guzy trzustki występują rzadziej, a wśród nich najczęstszymi są *gastrinoma* i *insulinoma*. Guzy wydzielające prolaktynę są stosunkowo najczęstszą przysadkową prezentacją choroby. Gen odpowiedzialny za powstanie zespołu MEN 1 jest zlokalizowany na chromosomie 11 w pozycji 11q13 i koduje białko nazywane meniną, które wchodzi w reakcje z różnymi białkami biorącymi udział w regulacji transkrypcji, podziału komórek i naprawie DNA. Mimo opisania różnych mutacji w genie meniny, nie znaleziono do tej pory ścisłej korelacji pomiędzy genotypem i fenotypem.
Opis przypadku: W pracy przedstawiono przypadek 31-letniego mężczyzny, prawnika, który miał zdiagnozowany zespół MEN 1 w wieku 21 lat, kiedy był operowany z powodu guza przysadki wydzielającego prolaktynę oraz z powodu nadczynności przytarczyc. W 2000 roku wysunięto podejrzenie *insulinoma* i stwierdzono wieloogniskowe zmiany w trzustce. Jednakże pacjent nie zgodził sie na leczenie operacyjne. Od tej pory chory był leczony diazoksydem. U pacjenta obserwuje się stopniową progresję choroby, ale chory pozostaje w relatywnie dobrej kondycji fizycznej.
Wnioski: Badania przesiewowe w kierunku zespołu MEN 1 są szczególnie ważne u młodych chorych z guzami przysadki. Regularne wizyty kontrolne są bardzo istotne nawet po leczeniu chirurgicznym. U prezentowanego pacjenta stopniowo powiększają się zmiany w trzustce, również zaobserwowano nawrót nadczynności przytarczyc. **(Endokrynol Pol 2010; 61 (2): 212–216)**

Słowa kluczowe: *zespół MEN 1, insulinoma, menina, mutacja*

Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is a rare autosomal dominant inherited endocrine disorder characterized by pancreatic, parathyroid, and anterior pituitary tumours. Hypercalcaemia due to parathyroid tumours is usually the first manifestation of MEN 1 and occurs in 90% of patients. Pancreatic islet tumours are less frequent and are found in 40% of cases. Gastrinomas with Zollinger-Ellison syndrome are the most com-

Marcin Dębski M.D., Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Banacha 1a, 02–097 Warsaw, Poland, tel.: +48 22 599 12 63, +48 507 196 681, fax: +48 22 599 19 75, e-mail: debskim@wp.pl

mon. Insulinomas are the second most common, leading to hypoglycaemia, which is the cause of episodes of fainting. Prolactinomas are a pituitary presentation of the syndrome in 30% of cases [1]. Other organs such as the thymus, the adrenal glands, and the skin are involved less frequently [1, 2].

The tumour suppressor gene causing MEN 1 has been localized to chromosome 11q13. It is composed of 10 exons of total length 1,830 bp and the protein product of the *MEN 1* gene is named menin. Not only have several benign polymorphisms within the exons and introns of the *MEN 1* gene been found, but approximately 500 different germline mutations have been identified as well [4]. The protein, which is 610-amino acids long, is encoded by exons 2 to 10. It does not exhibit any apparent sequence similarity to other known proteins [5]. The biological role of menin remains unclear. The protein is located mainly in cell nuclei. Involvement in cell proliferation and division, and DNA repair seems possible as menin interacts with transcription factors such as: JunD, histone deacetylases and histone methyltransferases. Menin also interacts directly with oestrogen receptor α in a hormone dependent manner [3].

Heterozygous germline mutations of the *MEN 1* gene have been found in 90% of families with MEN 1 syndrome. However, some germline *MEN 1* mutations are also identified in patients with clinical presentation suggesting MEN 1 but who do not meet the exact criteria of the syndrome; for instance familiar isolated hyperparathyroidism [3]. Various types of mutations have been described. Frameshift mutations account for 50% of the mutations, nonsense for 20%, and splice site for 10%, respectively. These mutations cause premature termination of protein translation [6].

Clinical presentation of MEN 1 is very heterogeneous. Genotype-phenotype correlations have been postulated for many years, but thus far no strict relationships have been proven. A higher frequency of prolactinoma has been noticed in some ethnic groups with MEN 1, but it is unlikely that a certain type of mutation is responsible for such pituitary tumours [7]. Almost half of MEN 1 cases are diagnosed with pancreatoduodenal endocrine tumours, which are determinants of long-term survival. About one-third of patients develop malignant tumours with liver metastases [2]. Surgery is the treatment of choice for insulinomas, regardless of their size [8].

Here we report the case of a 31-year-old man with MEN 1 and multifocal insulinomas who did not agree to be operated and has been followed up for nine years.

Case report

A 21-year-old male was admitted to our department in 1999 after emergency surgery due to bleeding into a pituitary tumour, which was afterwards diagnosed as prolactinoma. As the prolactin (PRL) concentration was elevated — 111.74 ng/mL (reference values 1.4–24.2) — and MRI revealed the remains of the tumour, bromocriptine treatment was introduced, reducing PRL to normal values. Further investigation revealed increased concentrations of both calcium — 3.04 mmol/L (reference values 2.25–2.75) — and parathormone (PTH) — 150 pg/mL (reference values 10–70). The ^{99m}Tc MIBI scan was contributory as the focus of high MIBI absorption was found below the left thyroid lobe (Fig. 1). Primary hyperparathyroidism as a part of MEN 1 syndrome was diagnosed and the patient was referred to the surgery department. An attempt to remove 3 and ¾ of the fourth parathyroid glands was performed. However, pathological examination confirmed removal of only 2 specimens of parathyroid tissues: one adenoma and one hyperplastic gland, yet calcium and PTH concentrations returned to normal values.

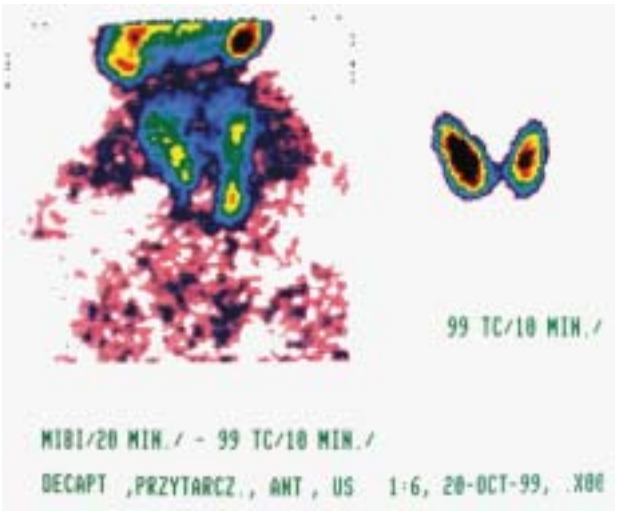

Figure 1. *^{99m}Tc MIBI scan of parathyroid glands*
Rycina 1. *Badanie scyntygrafii ^{99m}Tc MIBI gruczołów przytarczycznych*

The patient had never suffered from fainting or seizures and his glucose and insulin concentrations were normal. To exclude insulinoma, a fasting test was performed. On the second day, symptomatic hypoglycaemia of 1.22 mmol/L occurred with an insulin level of 14.4 mIU/mL (reference fasting range 6–20 mIU/mL). CT of the abdomen revealed a single lesion in the pancreas (Fig. 2), but the patient did not agree to be operated.

During the next hospital stay in 2001, ^{111In}octreotide scintigraphy showed two foci of abnormal absorption in the medial line (Fig. 3). Serotonin and 5-hydroxyindoleacetic acid levels were normal. Half a year later, in MRI scans, at least two pathological lesions were visible (Fig. 4). The patient again did not give agreement

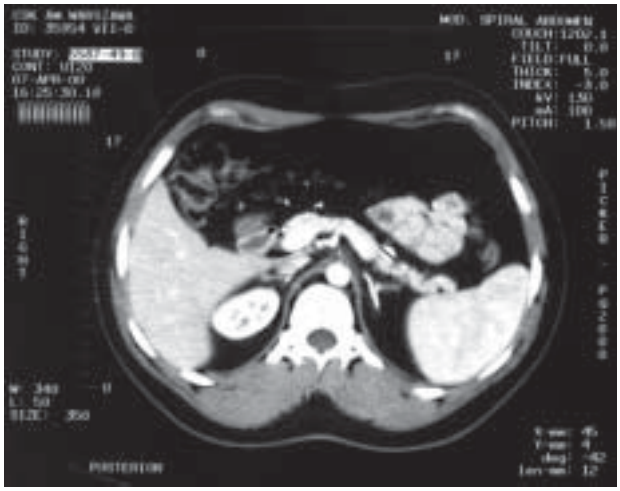

Figure 2. *Computed tomography of the abdomen showing single lesion in the pancreas*

Rycina 2. *Badanie tomografii jamy brzusznej pokazujące pojedynczą zmianę w trzustce*

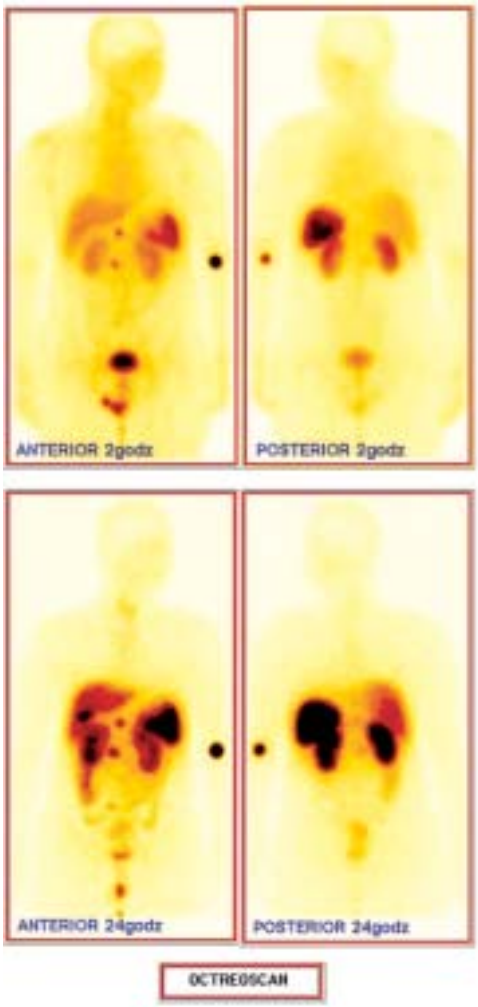

Figure 3. *^{111In}octreotide scintigraphy with 2 abnormal foci in median line in 2001*

Rycina 3. *Scyntygrafia z oktreotydem (2001 rok) z 2 nieprawidłowymi ogniskami w linii pośrodkowej*

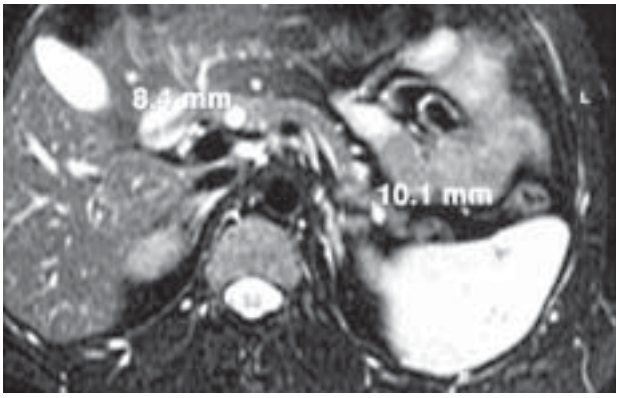

Figure 4. *Magnetic resonance imaging of the pancreas revealing 2 pathological lesions*

Rycina 4. *Rezonans magnetyczny trzustki ukazujący 2 patologiczne zmiany*

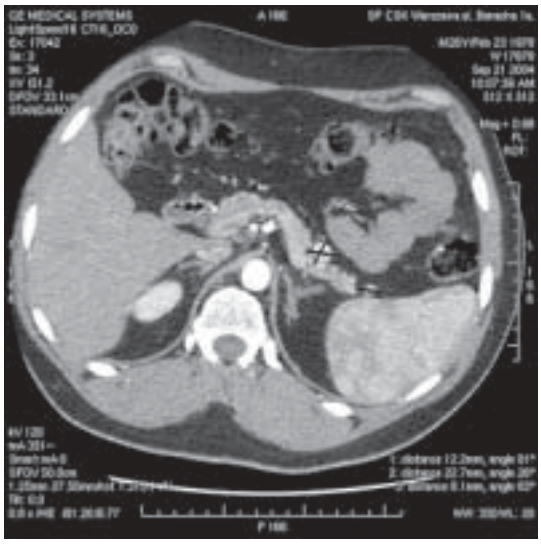

Figure 5. *Computed tomography of the abdomen showing further growth of the lesions (year 2004)*

Rycina 5. *Tomografia komputerowa jamy brzusznej ukazująca dalszy wzrost zmian (2004 rok)*

for surgical procedures. As his fasting glucose was 3.33 mmol/L, diazoxid treatment was initiated. The patient started studying law. Three years later, CT imaging confirmed the growth of pancreatic lesions, but there were no signs of lymph nodes or liver infiltration (Fig. 5).

At present, CT reveals gradual enlargement of multifocal insulinomas with no metastasis into the liver (Fig. 6). Serum calcium concentration is 2.76 mmol/L and PTH is 144.8 pg/mL. Moreover, a ^{99m}Tc MIBI scan showed pathological focal tracer concentration uptake below the right thyroid lobe (Fig. 7). Prolactin remains within normal values on 5 milligrams of bromocriptine daily. Insulin is 15.4 mIU/mL with no episodes of hypoglycaemia on diazoxid treatment. For nine years of follow up the patient

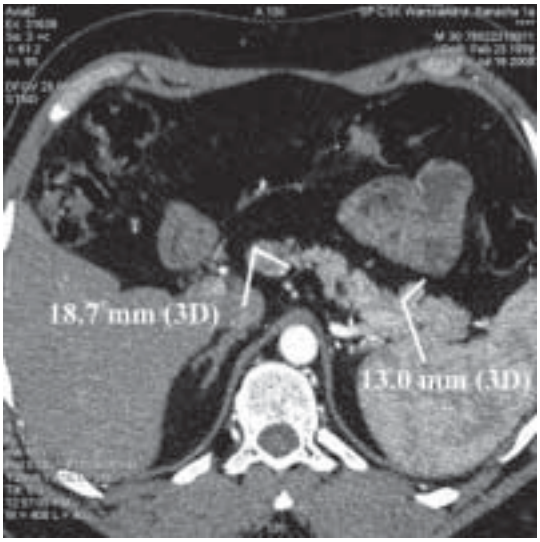

Figure 6. *The latest visualization of pancreatic lesions*
Rycina 6. *Ostatnia wizualizacja zmian w trzustce*

has never suffered from episodes of fainting nor lost consciousness. He still refuses surgical intervention. Interestingly, the patient has already finished his law studies and has become successful lawyer.

Discussion

We described a 31-year-old man with MEN 1 syndrome after pituitary surgery for prolactinoma and parathyroid gland surgery because of hyperparathyroidism. Coexisting multifocal insulinoma was diagnosed. However, the patient refused operative treatment of insulinoma and this is the reason why we present nine years of follow up.

Neuroendocrine tumours of the pancreas account for 2–10% of all pancreatic neoplasms [9]. Insulinomas are of benign character in 90% of cases, but the rest are malignant with a life expectancy of 2.5–3 years. Long-term survival after surgical treatment is 5 years [10]. Operation and removal of the lesion is the treatment of choice in case of functioning pancreatic tumours [11] as these neoplasms are determinants of long-term survival. There are no clear markers of malignancy. Assessment of mitotic index and Ki-67 expression has some prognostic value. The extent of surgery has not been fully established. Simple enucleation of the lesion is not always possible. The younger the patient is, the more pancreatic tissue must be preserved to prevent postoperative diabetes. Waldmann et al. described the case of a 37-year-old man with MEN 1 syndrome who devel-

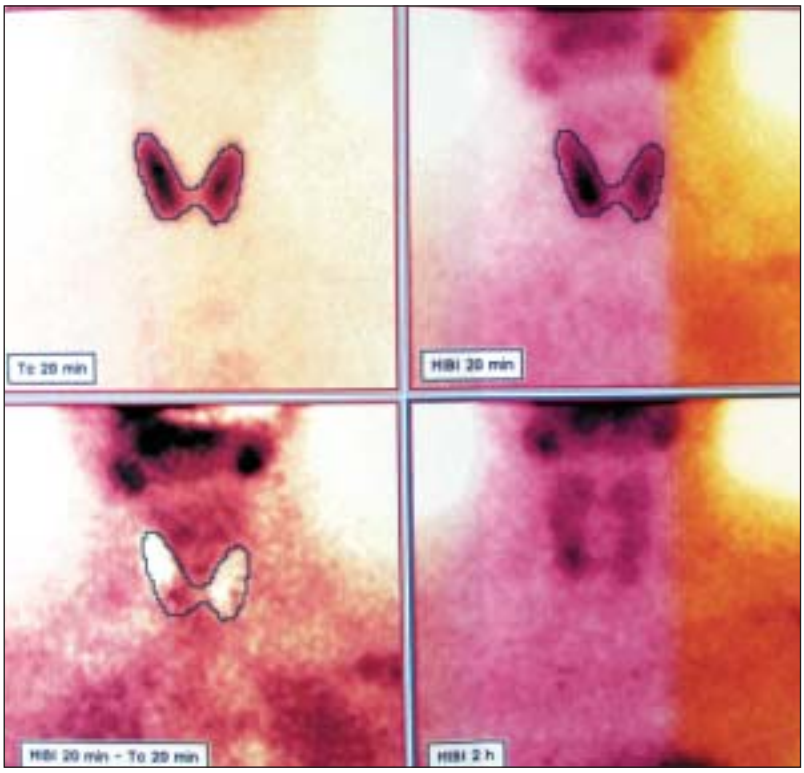

Figure 7. *The latest ^{99m}Tc MIBI scan of parathyroid glands*
Rycina 7. *Ostatnia scyntygrafia ^{99m}Tc MIBI gruczołów przytarczycznych*

oped a fast-growing neuroendocrine carcinoma. The author suggests more frequent follow-up to detect the early stage of tumour development [2].

As far as pharmacological treatment is concerned, diazoxid is the treatment of choice. This agent inhibits insulin secretion via direct action on β islet cells [10]. The most common side effects are oedema, weight gain, and renal dysfunction. That is why sometimes diuretics are added to this treatment. Somatostatin analogues, like octreotide and lanreotide, may also be considered in the treatment of tumours which express somatostatin receptor type 2. However, in some cases they may intensify hypoglycaemia because of the suppression of growth hormone secretion [10, 12, 13]. In a few cases, interferon α may be useful. The median duration of response is 8.5 months, but all patients improve clinically [14]. There are very scarce data of the methods and results of chemotherapy in malignant insulinomas. For more aggressive tumours and metastatic disease, systemic chemotherapy is offered. The standard chemotherapy for neuroendocrine pancreatic tumours is a combination of adriamycin and streptozocine, and to a lesser extent a combination of 5-fluorouracyl and streptozocine [15]. As far as our patient is concerned, diazoxid was fully adequate as there were no episodes of hypoglycaemia and his cognitive function was good enough to allow him to graduate from law studies.

Heterozygous germline mutations of the *MEN 1* gene have been found in about 90% of familiar MEN 1 [3]. Nonetheless, more than 10% of cases do not have any mutation in the coding region of the *MEN 1* gene. Several mutation types have been identified, of which deletion is one of the most frequent. It often results in early termination of the protein. Such a type of mutation was found in two Italian monozygotic twins. There were some differences in clinical presentation in comparison with our patient. One of the two twins suffered from insulinoma, while the second was asymptomatic [16]. A novel 1113delC mutation was described in a 32-year-old male with: hypercalcaemia resulting in recurrent nephrolithiasis as a symptom of hyperparathyroidism, hypoglycaemia due to insulinoma, and microprolactinoma. Partial pancreatectomy was the method of treatment for insulinoma [17]. Intronic mutations also occur in MEN 1 syndrome. Turner et al. reported intron 4 mutations in seven unrelated families. The tumours in these families varied considerably, indicating a lack of genotype-phenotype correlation [18]. Such a correlation has been postulated for many years [1], but so far there has been no strong evidence. A subtype of familiar MEN 1 characterized by an unusually high incidence of prolactinoma and low frequency of enteropancreatic tumours has been noticed in the Burin peninsula, but it seems unlikely that particular MEN 1 mutations are responsible for this particular subtype [7]. Similarly, a group of 200 unrelated cases were investigated in the Swedish population. There was no correlation between the severity of the disease and the mutation type and location. A total of 69% of all mutations resulted in truncated protein. A total of 94% of all MEN 1 families had a mutation in the coding region of the MEN 1 gene [19]. Despite numerous investigations, a possible genotype-phenotype correlation is very difficult to assess.

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