Complete Remission of Recurrent Multiple Insulin-Producing Neuroendocrine Tumors of the Pancreas with Somatostatin Analogs: A Case Report and Literature Review

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Case Report

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Abstract

Hyperinsulinemic hypoglycemia is most commonly caused by a single, sporadic insulinoma. Multicentric insulinoma disease (insulinomatosis) as well as metachronous neuroendocrine tumors of the pancreas, known also as neuroendocrine adenomatosis, represent a very rare condition, if not associated with multiple endocrine neoplasia type 1 syndrome (MEN1) or Von Hippel Lindau disease.

We report a 9-year follow-up of a 41-year old woman, initially presenting with hypoglycemic syndrome caused by two insulin-producing tumors, who underwent subtotal pancreasectomy in 2012, with histology compatible with multiple small neuroendocrine tumors. An approximately 1 centimeter insulin-producing tumor recurred at subsequent biochemical and radiological follow-up, and was cured with the somatostatin analog octreotide as a single treatment, until remission of symptoms and complete regression of the pancreatic lesion achieved after only 16 months of treatment.

The possible mechanisms for these findings are discussed and the literature is briefly reviewed.

Introduction

Insulinomas are the most frequent cause of hyperinsulinemic hypoglicemia. They are usually benign sporadic tumors, but in about 10% of the patients they may be associated with hereditary diseases, such as multiple endocrine neoplasia type 1 (MEN1) [1]. Insulinomatosis is a very rare neoplastic condition defined by the presence of multiple small and large insulin-producing tumors, which synchronously and metachronously develop within the pancreas. In patients affected by this disease, hyperinsulinemic hypoglycemia typically recurs after removal of the visible lesions. The pathophysiolgy of this condition shows that the insulin-producing tumors are preceded by an insulin cell hyperplasia of the beta-cells of the pancreas [2, 3]. At the present, due to the rarity of the disease, no genetic defect are known, although a genetic missense mutation has been proposed in a recent study [4].

Medical therapy for patients with neuroendocrine neoplasms (NEN), including insulin-producing ones, is aimed to decrease the circulating hormones which cause typical syndromes and control of tumor growth.

Approximately 50% of insulinomas express somatostatin receptors on their cells' surface, mainly receptor subtypes 2 and 5. The somatostatin analogs octreotide and lanreotide are able to inhibit the signal-transmission pathways by binding these receptors [5].

We report a case of hyperinsulinemic hypoglycemia caused by multiple recurrent small insulin-producing tumors which recurred after surgery and responded to somatostatin analog treatment with complete remission of symptoms and regression of the pancreatic lesions.

Case Report

A 41-year woman presented as an outpatient to our Hospital in November 2012 for her annual thyroid condition follow-up (simple goiter associated with autoimmune chronic thyroiditis), complaining of neurological symptoms such as poor cognitive abilities and decreased alertness over the previous two years, sometimes associated with sweating and sudden hunger. During one of these episodes, the laboratory workout revealed low capillary blood glucose levels (36 mg/dl). On the suspicion of hypoglycemic syndrome, the patient was admitted to the Endocrine Unit of Forlì Hospital. At the physical examination her weight was 70 Kg and BMI 24.5; blood pressure was 110/70 mmHg and no abnormalities were found at abdominal, cardiac, pulmonary and neurological examination. Other causes of hypoglycemia were also excluded upon admission, namely exogenous insulin and oral hypoglycemic agent administration, as well as insulin autoimmune syndrome (Hirata disease), as insulin autoantibodies were negative.

A supervised 72-hour fasting test was performed, showing low venous glucose values (43 mg/dl; Fig. 1) and increased levels of insulin (3.7 mU/L) and C-peptide (0.43 nmol/L). The test was interrupted at the sixth hour and sugar was administered orally.

An abdominal CT scan revealed 2 lesions located within the body-tail of the pancreas, measuring 16 mm and 8 mm, respectively, and presenting contrast enhancement features typical of insulinomas (Fig. 2).

Subsequently, a 68Ga-DOTATOC positron emission tomography was performed, showing high expression of somatostatin receptors on the surface of the two above-mentioned pancreatic lesions, confirming the presence of neuroendocrine tumors (Fig. 3).

An extensive review of both personal and family history of the patient did not suggest the presence of MEN1. Circulating levels of parathormone and serum calcium, as well as prolactin, adrenocorticotrophic hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, growth hormone, and insulin-like growth factor 1 were normal in two different determinations. Additional diagnostic evaluation for MEN1 syndrome, such as magnetic resonance imaging (MRI) of the sella turcica and parathyroid scintigraphy, were also negative.

In December 2012, subtotal pancreasectomy was performed, and detailed histopathological examination revealed 2 tumors measuring 16 and 10 mm in the pancreatic body-tail along with several other small tumors (< 0.5 cm; Fig. 4). The immunohistochemistry staining for insulin (Fig. 5), chromogranin A (clone LK2H-10, Ventana Roche Diagnostics, Fig. 6), somatostatin receptors (Fig. 7, panel A), and synaptophysin (Fig. 7, panel B) was strongly positive. The proliferation activity examined with a commercial monoclonal anti-Ki-67 antibody (MIB-1, DAKO, Denmark) was 1% (Fig. 8) The histology was therefore compatible with multiple well differentiated neuroendocrine neoplasms, according to the World Health Organization grade 1 [6].

Clinically, the patient presented no symptoms of hypoglycemia, and blood sugar levels measured after surgery were within the normal range. She was therefore discharged from the surgical ward and no pharmacological treatment was given.

In January 2013, germline mutation analysis of the MEN1 gene was conducted at the University Hospital of Ferrara, Italy. DNA preparation, amplification of exons 2 and 10 of the MEN1 gene, denaturing gradient gel electrophoresis, single-strand conformation polymorphism analysis, and sequencing analysis of the MEN1 gene were performed and showed no mutations.

After one year (November 2013), computed tomographic scanning demonstrated a 10 mm lesion within the body of the pancreas, showing the same enhancing features typical of neuroendocrine tumors. Hence, a 68Ga-DOTATOC positron emission tomography was performed, showing moderate uptake of the radioligand at the level of the above described lesion. An FDG positron emission tomography was also performed which showed no uptake in the pancreas or other abdominal and extra-abdominal sites. Pancreatic ultrasound endoscopy confirmed the presence of a 13 mm tumor located in the body of the pancreas.

In January 2014, another supervised 72-hour fasting test was performed at the Endocrine Unit of Forli Hospital, showing low venous glucose values (42 mg/dl; Fig. 1) and increased levels of insulin (8.7 mU/L; Fig. 9) and C-peptide (0.43 nmol/L). The test was interrupted at the sixty-eighth hour (Fig. 1), even though the patient presented no symptoms of hypoglycemia.

The case was repeatedly discussed by the Multidisciplinary Medical Team for Management and Treatment of Neuroendocrine Tumors of Romagna both in January and February 2014. Various medical strategies were suggested, including a second surgical approach, radiolabeled target therapy and diazoxide treatment. However, the patient refused to undergo further surgery and other specific treatments with possible side effects. In February 2014, after seeking internationally recognized professional expert opinion (Kjell Oberg, University Hospital of Uppsala, Sweden), medical treatment with the somatostatin analog octreotide (30 mg given intramuscularly every 28 days) was started and regularly administered during the subsequent follow-up.

In the following 6 months, the patient did not show any symptoms or signs of hypoglycemia and the treatment with octreotide was tolerated without particular side effects. The plasma levels of chromogranin A, glycemia and insulin were within the normal range. The abdominal MRI performed in July 2014 showed a 12 mm angioma of the liver and apparently no lesions of the pancreas.

In November 2015, a CT scan of the abdomen was performed, showing no lesions within the pancreas and confirmed the presence of a stable angioma of the liver.

A second opinion was given by the Oncological Centre of Milan, confirming the treatment with somatostatin analogs, which was eventually discontinued in September 2016, because the patient's desire for pregnancy.

A 68Ga-DOTATOC positron emission tomography performed in September 2018 showed no uptake of the radioligand.

In October 2018, pancreatic ultrasound endoscopy confirmed the absence of lesions in the head-body of the pancreas.

In the following years until April 2021, the patient continued with regular 6-month clinical check-ups, including measurements of basal glycemia, insulin, C-peptide and chromogranin A, which were always unremarkable, and annual imaging techniques, both with CT scans of the abdomen (Fig. 10) and MRI of the abdomen. All the results were completely negative for recurrent disease.

In April 2021 the patient was admitted to Endocrine Unit of Forli Hospital in order to perform once again a supervised 72-hour fasting test, about 9 years after the first one: the venous glucose values were never below 45 mg/dl and the levels of insulin (4.5 mU/L) and C-peptide (0.26) measured at the lowest sugar levels were not consistent with recurrency (Fig. 1 and Fig. 9). The test was not interrupted and the patient showed no symptoms of hypoglycemia, indicating complete remission of the insulinoma syndrome.

The patient now continues with the regular follow-up, remaining asymptomatic and taking no specific medical treatment.

Discussion

To our knowledge, this is the first described case of a primary neuroendocrine tumor of the pancreas without metastasis that was completely cured with medical therapy after recurrent disease. We report a rare case of severe hypoglycemia caused by multiple small insulin-producing neoplasms which recurred after surgery and responded to somatostatin analog treatment with complete remission of symptoms and regression of recurrent disease.

Insulinomas, which are the most frequent cause of the hypoglicemic syndrome due to hyperinsulinemia, are generally benign tumors with a median age of onset of 47 years and a 5-year survival rate of 100%, but sometimes display malignant behavior (less than 10%). In about 10% of patients, insulinoma can be associated with MEN1 and very rarely with Von Hippel-Lindau syndrome. The clinical scenario at diagnosis is the Whipple triad, i.e. symptoms or signs consistent with hypoglycemia, plasma glucose level less than 50 mg/dl and relief of symptoms after glucose administration. Hypoglycemic episodes occur mostly during fasting periods and sometimes during the post-prandial phase [7, 8]. The diagnosis must be confirmed with a supervised 72-hour fasting test [9], although a 48-hour fasting test has also been suggested [10].

Another interesting and very rare pathological condition in our case is the presence of pancreatic neuroendocrine microadenomatosis and, more specifically, insulinomatosis. This is a neoplastic pancreatic disease in which synchronously and metachronously, multiple small and large insulin-producing tumors develop [11]. These patients present with hyperinsulinemic hypoglycemia which, after removal of the visible lesions, typically recurs[12]. It seems that the tumors are preceded by an insulin cell hyperplasia of the beta-cells of the pancreas.

Pancreatic neuroendocrine tumors measuring less than 0.5 cm are classified as neuroendocrine microadenomas. Multiple neuroendocrine microadenomas are called neuroendocrine adenomatosis. The prevalence of this condition is very low and may occur sporadically or associated with the above-mentioned genetic syndromes as for insulinomatosis [13]. As for all the neuroendocrine tumors, even microadenomatosis may be clinically silent or present with typical hypersecretive syndrome, as described by Alencar N. et al [14].

Somatostatin receptors are expressed on the cell surface of approximately 80% of NENs and 50% of insulinomas, allowing somatostatin analogs octreotide and lanreotide to bind to receptor subtypes 2 and 5 [15]. Thanks to the inhibition of the signal-transmission pathways mediated by somatostatin receptors, tumor-related syndromes are amelioreted and tumor growth is stabilized [16].

Somatostatin analogs are the second-line medical treatment for controlling hypoglycemia in patients with insulinomas, mainly for malignant insulinomas with recurrent hypoglycemic events. Octreotide was shown to be effective in controlling hypoglycemia in 59% of patients with insulinomas [17]. Other medical treatment options include the other first generation somatostatin analog lanreotide LAR, the second generation somatostatin analog pasireotide, as well as everolimus and chemotherapy, including temozolamide. However, in insulinomas without somatostatin receptor expression, somatostatin analogs may worsen hypoglycemia by inhibiting counter-regulatory mechanisms, namely glucagon and growth hormone release [5].

Although somatostatin analogs were developed primarily for reducing the levels of circulating hormones causing typical endocrine syndromes, the results of PROMID [18] and CLARINET [19] studies confirmed that somatostatin analogs have a positive impact on progression-free survival in pancreatic and non-pancreatic neuroendocrine tumors, due to their anti-proliferative effect [20]. This is owed to somatostatin receptor density on the neoplastic cells that allow the treatment with somatostatin analog octreotide to be effective.

Interestingly, in our case not only was there a complete remission of the symptoms after starting the somatostatin analog octreotide, but also the antiproliferative effect on the 10 mm lesion of the pancreas was observed. As a matter of fact, no lesions were visible at abdominal CT scan or MRI, nor at endoscopic ultrasonography, which has a very high diagnostic accuracy of about 98%, after a total of 16 months of treatment.

In summary, we describe a rare case of a patient with hypoglycemic syndrome caused by multiple neuroendocrine tumors of the pancreas (insulinomatosis). The response obtained by antineoplastic treatment resulted in tumor load decrease up to complete remission of the disease; the use of somatostatin analogs in treating single or multifocal insulinomas as well as functioning and non-functioning neuroendocrine multiple subcentimetric tumors should thus be considered as a pharmaceutical option, when surgery is not possible or surgical eradication is not achieved.

Declarations

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Author contributions

Andreas Tartaglia wrote the main manuscript, acquisition and interpretation of data. Giulia Busonero made substantial contributions to the conception and design of the work. Valentina Boddi and Lorenza Gagliardi revised it critically for important intellectual content. Maurizio Nizzoli gave final approval of the version to be published. All authors read and approved the final manuscript. Funding: no funding.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

The medical treatment and the use of data were approved by the principles of the Declaration of Helsinki.

Authors' disclosures of potential conflicts of interest

The authors declare no potential conflicts of interest.

Statement of Ethics

Written informed consent to participate was obtained from the patient and for publication of this case report and any accompanying images.

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Figures

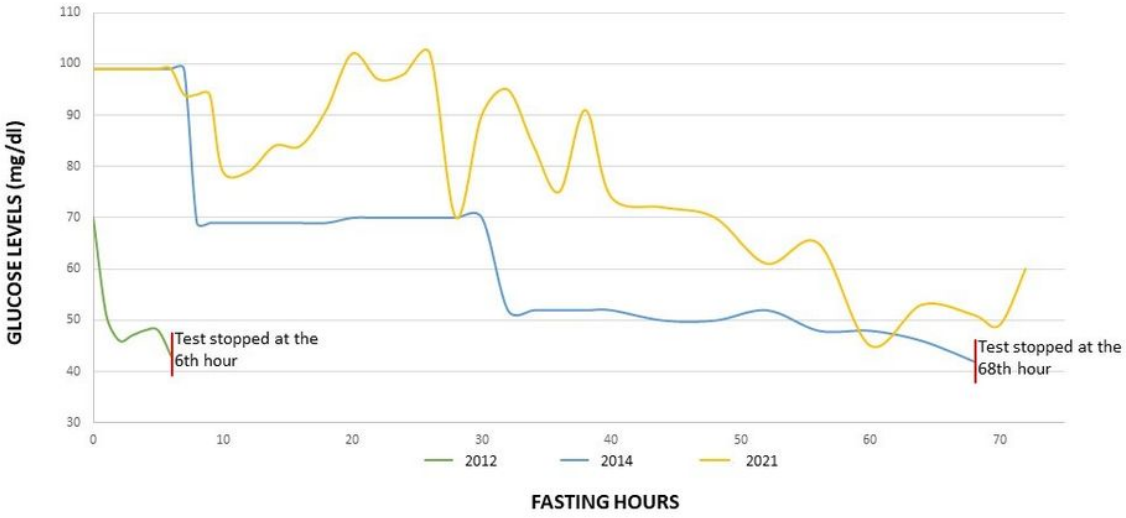

Figure 1

Comparison of glucose levels between 2012, 2014 and 2021 fasting tests

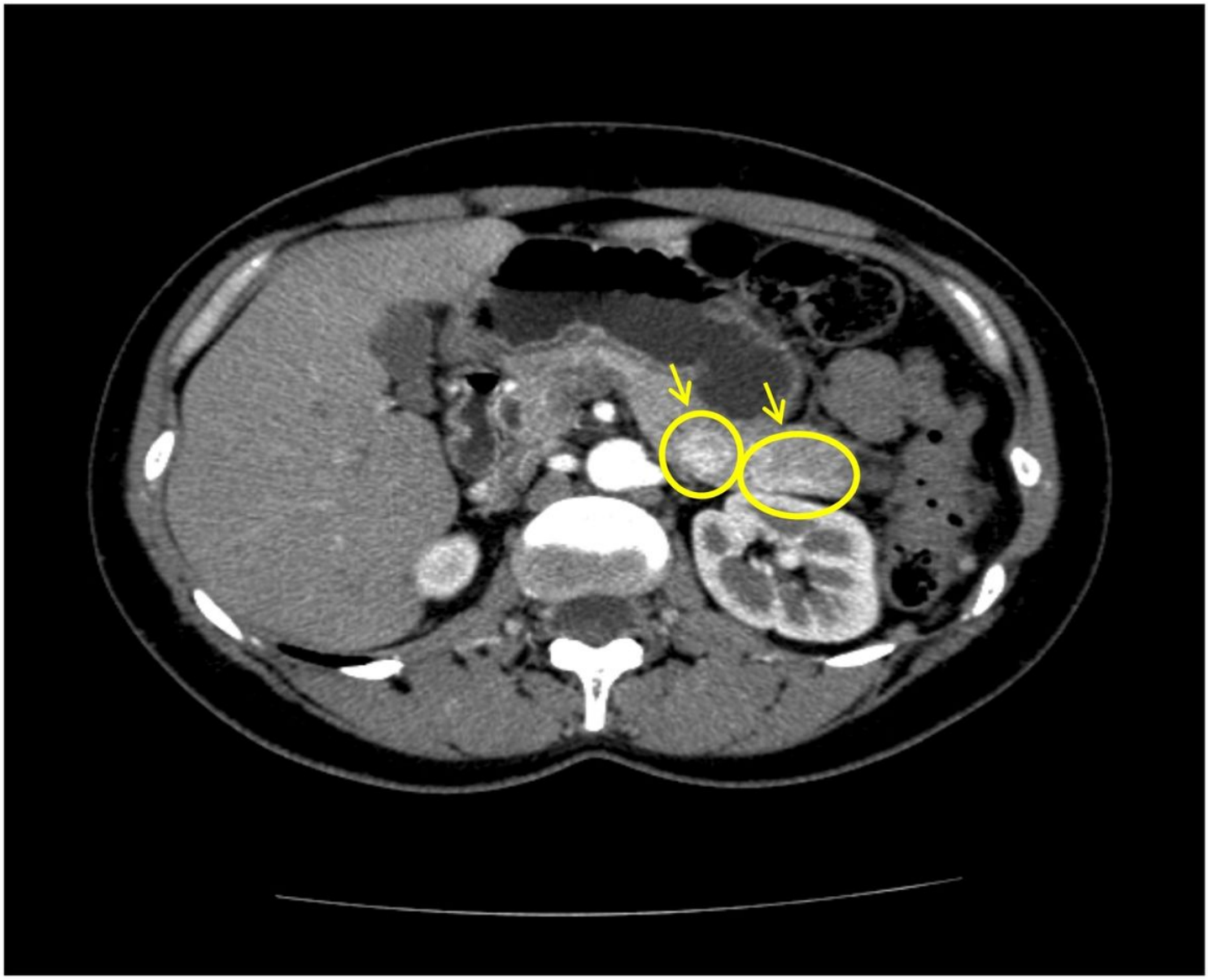

Figure 2

CT scan showing two lesions in the body of the pancreas (marked with yellow arrows and circles)

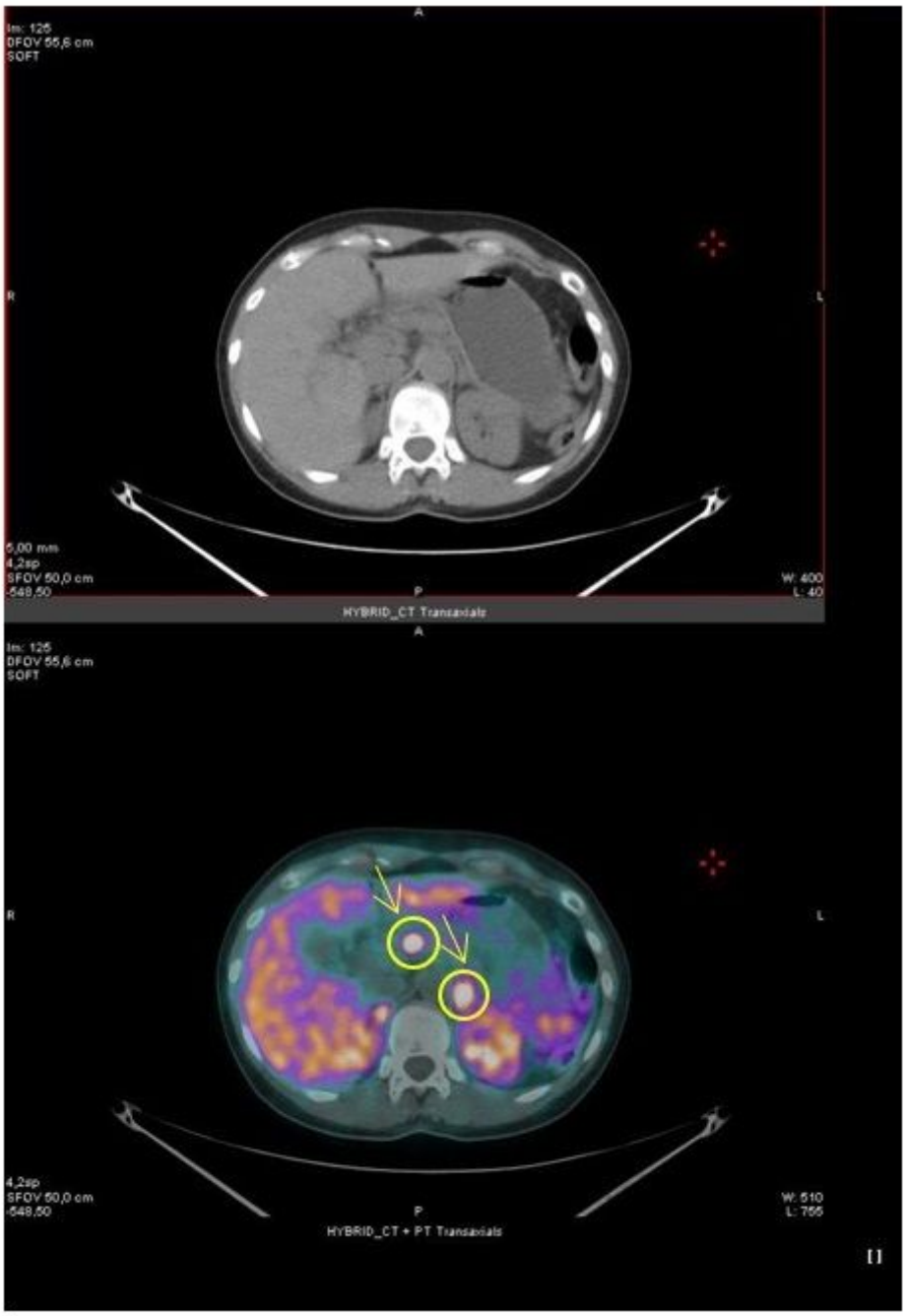

Figure 3

68Ga-DOTATOC PET imaging showing two pancreatic body lesions with a standardized uptake value of 12 (marked in yellow arrows and circles).

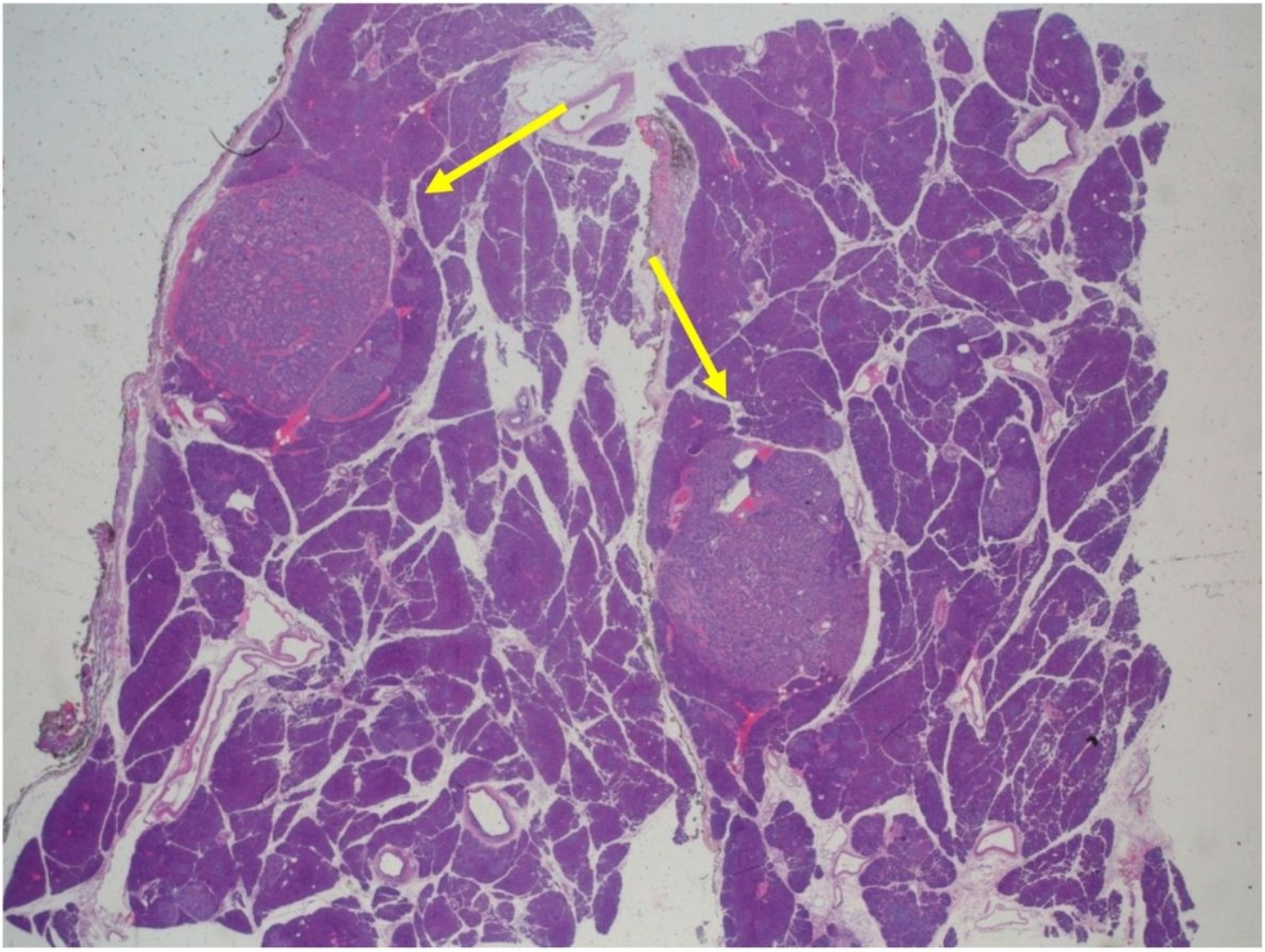

Figure 4

Histology of multiple neuroendocrine tumors of the pancreas with hematoxylin and eosin staining (panoramic view).

Figure 5

Histology of the insulinomas at 2X power. The upper panel (A) shows hematoxylin and eosin staining and the lower panel (B) shows immunihistochemestry staining for insulin.

Figure 6

Histology of the insulinomas: immunohistochemistry staining for chromogranin A.

Figure 7

Histology of the insulinomas: immunostaining for somatostatin receptor type 2 (panel A) and synaptophysin staining (panel B).

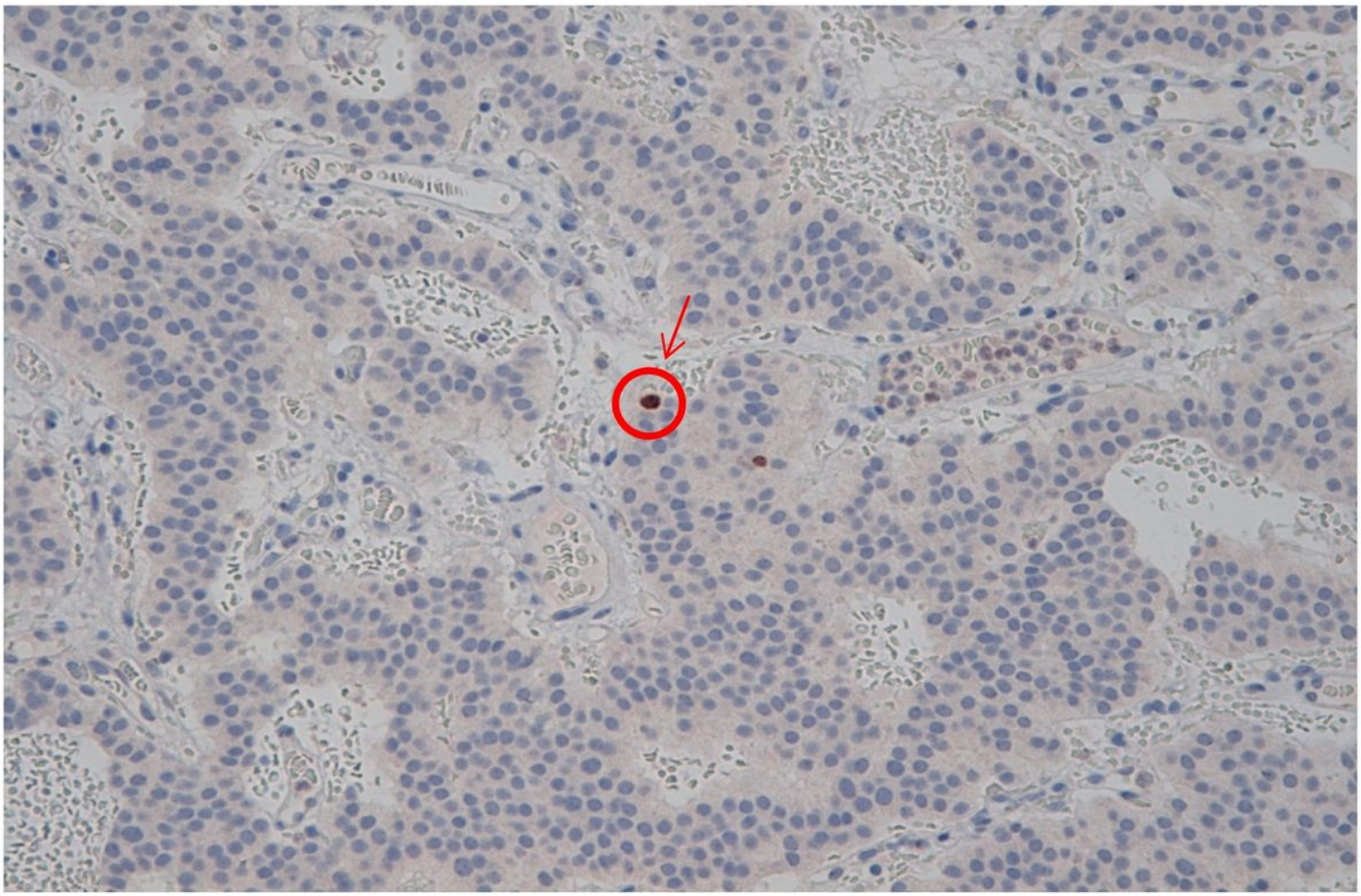

Figure 8

Histology of the insulinomas; Ki67 immunostaining (marked with red arrow and circle).

Figure 9

Comparison of insulin levels between 2014 and 2021 fasting tests

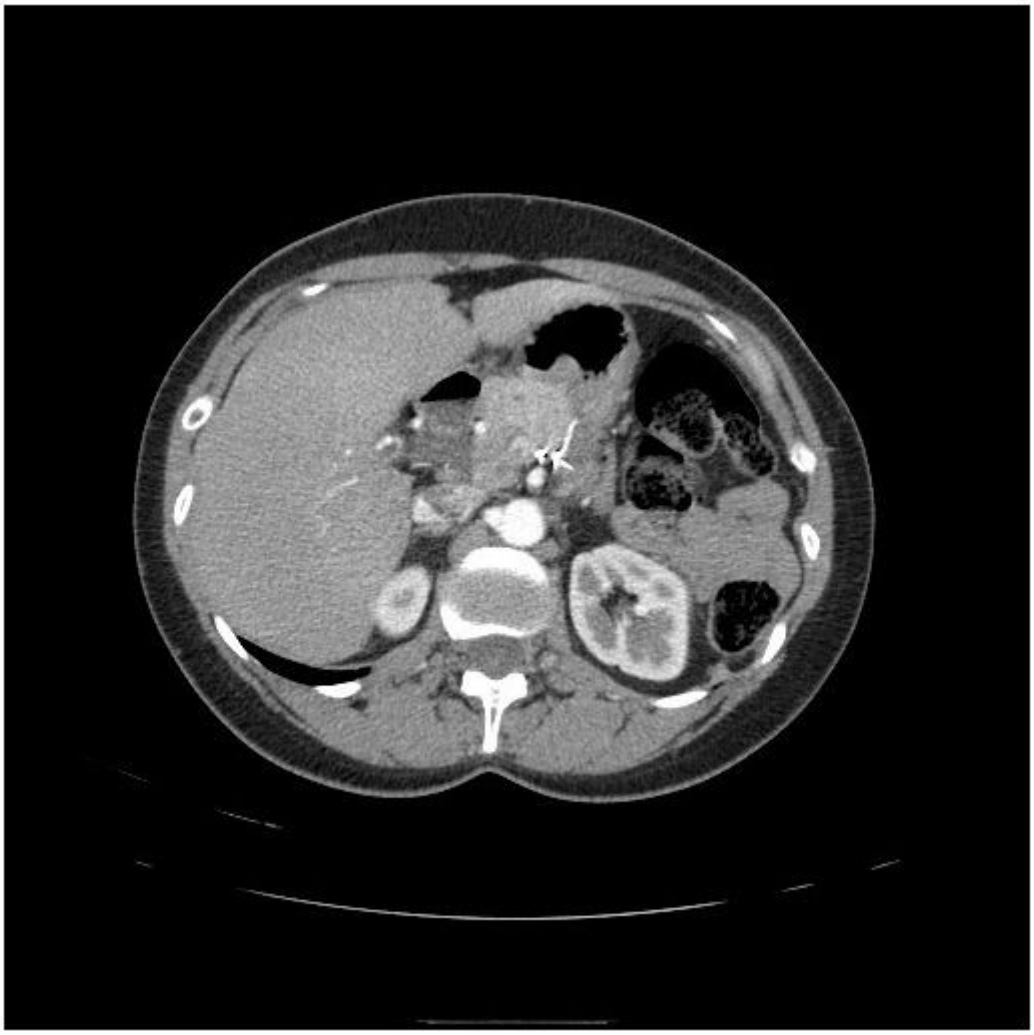

Figure 10

CT scan showing no lesions of the pancreas