

Combined Biological Therapy is Effective to Control all Neuroendocrine Tumor Manifestations in a Patient with MEN1 Syndrome

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome predisposing to the development of many endocrine tumors. Mainly pituitary, parathyroids and pancreas are involved although a proliferative state interests all neuroendocrine system. MEN1 pancreatic neuroendocrine tumors (pNET) are multiples and can secrete different hormones resulting in specific endocrine syndrome. The therapeutic approach is based in surgery which usually is followed by tumor relapse or persistence unless to be highly aggressive. Biotherapy with somatostatin analogs (SSAs) and dopamine agonists could be of great benefit to manage these patients without altering their life quality.

We report a case of a 36-year-old MEN1 man affected with multicentric PNETs associate with insulinoma and Zollinger-Ellison syndrome, pituitary prolactinoma and primary hyperparathyroidism. Therapy with symptomatic agents (proton pump inhibitors, diazoxide) as well as biotherapy (lanreotide, cabergoline) was started. At six month follow-up, symptomatic agents were stopped and disease control was only based on lanreotide plus cabergoline. This combined biotherapy was able to control endocrine syndromes and tumor growth, resulting in the possibility to perform a safer and selective surgical intervention on pNETs. Somatostatin and dopamine receptor expression has been evaluated and related to clinical response to biotherapy.

Therapy with lanreotide and cabergoline was able to control multiple secreting tumors in a patient with MEN1, due to high expression of specific receptors. The combined use of somatostatin analogues and dopamine agonists is suggested in patients with MEN1.

Keywords: MEN1 syndrome; Neuroendocrine tumors; Insulinoma syndrome; Zollinger-Ellison syndrome; Prolactinoma; Somatostatin analogues; Dopamine agonists

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal-dominant hereditary syndrome [1]. Loss of the MEN1 tumor suppressor gene activity predisposes to the development of many endocrine and neuroendocrine tumors (NETs) and/or hyperplasia, involving mainly pituitary, parathyroids and pancreas [2] although a proliferative state interests all neuroendocrine system.

While primary hyperparathyroidism, due to parathyroid adenomas and hyperplasia, is the most common manifestations of the syndrome, prognosis is mainly related to the risk of malignant transformation and metastatic progression of tumors arising from pancreas [3]. Pancreatic NET (pNET) arising from islet cells may be nonfunctioning or functioning, with production of active hormones such as gastrin, insulin, vasoactive intestinal polypeptide (VIP), glucagon and somatostatin resulting in specific endocrine syndrome [4]. As opposed to their sporadic counterpart, MEN1 pNETs are characterized by early onset, multifocality, variable expression and propensity for malignant degeneration [5], making the management of MEN1 patients complicated and unpredictable. Therapeutic approach in MEN1-related tumors is based on surgery. However, there is a high risk of recurrence after surgical intervention, even after radical surgery [6,7]. On the other hand, surgery is accompanied by high morbidity especially for pNETs, which is also associated with risk of death or severe abdominal complications [8].

Medical therapy includes chemo- or biotherapy. It is generally assumed that chemotherapy is not effective in both sporadic and MEN1 NETs, since they are well differentiated slow proliferating tumors. Indeed, biotherapy with somatostatin analogs (SSAs) has been demonstrated to arrest tumor growth in well differentiated NETs [9,10]. Dopamine agonists (DAs) are effective in controlling tumor growth and hormone secretion in some pituitary tumors. Their activity in NETs is hypothesized on the basis of the reported expression of dopamine receptors in these tumors. Possible synergistic effects of SSAs and DAs could be of great benefit to manage MEN1 patients, either arresting tumor growth or maintaining unaltered quality of life.

In this case report, we describe a MEN1 man affected with prolactinoma, primary hyperparathyroidism, multiple pNETs associated with Zollinger-Ellison syndrome and insulinoma syndrome.

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He experienced an excellent response to therapy with lanreotide Autogel, a long-acting SSA. Since a concomitant therapy with the DA cabergoline was given for a PRL-secreting pituitary adenoma, the potential synergistic effects of lanreotide Autogel and cabergoline is discussed.

Materials and Methods

Hormone assay

Measurements of gastrin (Gastrin RIA kit; normal, <108 ng/ml), glucagon (Glucagon RIA kit; normal, <200 pg/ml), somatostatin (Somatostatin RIA kit; normal, <37 pg/ml), VIP (VIP RIA kit; normal, <31 pg/ml), insulin (BI-INSULIN IRMA kit; normal, <17 mU/L), chromogranin A (CGA) (CGA RIA kit; normal, <98 µg/L), ionized calcium (specific electrode ; normal, 1.12-1.30 mM/l), serum intact parathyroid (PTH) (PTH intact; normal, <70 pg/ml) and PRL (PRL; normal, <288 mU/L) were performed at the diagnosis and during the follow-up [11].

Morphofunctional study

A contrast-enhanced helical computed tomography (CT) was performed; 5 mm scans were acquired at 30 sec. after i.v. bolus injection (3 cc/sec) of 150 cc of iodinated non-ionic contrast media. A SST scintigraphy was performed using intravenous injection of Indium-¹¹¹-DTPA-Phe1-octreotide (Octreoscan, Mallinckrodt Medical, Petten, The Netherlands; 120-200 MBq), also performing an abdominal emission tomography (SPECT) at 24h. Tumor uptake was semi-quantitatively scored according to Krenning's scale [12].

Immunohistochemical study

Formalin-fixed paraffin-embedded sections of the endocrine pancreatic tumors were obtained to perform immunohistochemical study for neuroendocrine markers and specific pancreatic peptides. 5 µm thick tissue sections were deparaffinized, rehydrated and heated in a microwave oven in pH 6 citric acid buffer at 100°C for 15 min. After a wash in phosphate buffer solution, the sections were immersed for 15 min in a commercial serum-free protein block (DAKO, Cal, USA) for 20 min. Bound antibodies were revealed with a commercial peroxidase-labeled-streptavidin immunohistochemical kit (LSAB 2 DAKO). Aminoethylcarbazole (AEC) was used as chromogen. Finally, the sections were counterstained with hematoxylin and mounted in aqueous medium (Glycergel, DAKO). They were incubated overnight at 4°C in a humid chamber with the following primary antibodies. All tumor specimens were positive for CGA (monoclonal antibody, 1:200 dilution, DAKO Cytomation, Glostrup, Denmark) and synaptophysin (polyclonal antibody, 1:50 dilution, DAKO) and two specimens were positive for insulin (polyclonal antibody, 1:200 dilution, DAKO). One insulin-positive pancreatic tumor was evaluated for the expression of somatostatin receptor (SSTR) subtypes. SSTR2, SSTR3, SSTR5 immunostaining was evaluated by two operators (M.V., M.P.) using polyclonal antibodies (1:3000 dilution, Biotrend, Germany). Dopamine receptor subtype 2 (D2) immunostaining was also evaluated on the same insulin-positive pancreatic tumor according to the procedures described by Gatto et al. [13]. D2 immunostaining was evaluated by one operator (L.H.)

MEN-1 gene mutation analysis

To confirm the diagnosis of MEN1, germline mutation in the menin gene was searched in the proband as previously described [14]. A written informed consent had been obtained. Encoding

regions (exons 2 to 10) and intron-exon junctions of the MEN1 gene were examined. The obtained sequences were compared to wild type reference sequence of the MEN1 gene (Sequence number U93237). A novel heterozygote frameshift 335delA mutation in the exon 2 was revealed in the proband. The study was performed in accordance with the Helsinki declaration on human experimentation.

Case Presentation

A 36-year-old man presented with symptoms of neuroglycopenia. At the anamnesis, there was a history of kidney stones and dyspeptic syndrome with post-prandial swelling and heartburn since five years before. Physical examination revealed sweating and tachycardia. Biochemical assessment showed hypoglycemia and not suppressed insulin and C-peptide levels (Figure 1, Basal). Sideropenic anemia and hypophosphatemic hypercalcemia were also found. A fasting test confirmed the clinical diagnosis of insulinoma by revealing insulin to glycemia ratio of 0.6 and C-peptide serum concentrations of 6.0 ng/ml in condition of hypoglycemia. To localize the insulin-secreting primary tumor, a contrast-enhanced CT scan was performed and detected 4 nodules ranging 10-25 mm along head, body and tail of the pancreas. A complete hormonal and instrumental work-up was performed to characterize the pancreatic lesions and to screen for a MEN1 syndrome. High plasma levels of CGA (not shown) and gastrin (Figure 1) were found and associated, at the endoscopy, to an erosive gastro-duodenitis. A pituitary microadenoma was also detected at the MRI and characterized by PRL hypersecretion (Figure 1), while primary hyperparathyroidism (PTH=15.8 pmol/L) with a mild increase of serum calcium levels (2.6 mmol/L) was associated to a left inferior parathyroid adenoma, as found at cervical doppler ultrasonography and sestamibi SPECT scintigraphy. A whole body Octreoscan pointed out a strong epigastric uptake corresponding to the greatest pancreatic lesion seen at the CT scan. On the basis of these findings, the diagnosis of insulinoma syndrome, Zollinger-Ellison syndrome, microprolactinoma and primary hyperparathyroidism was made. This picture was consistent with the diagnosis of MEN1 syndrome. A genetic test revealed an exon 2 MEN1 germline mutation.

In order to control the Zollinger-Ellison syndrome, a treatment with proton pump inhibitor (omeprazole) was started at the dose of 20 mg twice a day followed by a rapid improvement of gastric symptoms. One week later, diazoxide (300 mg a day divided in 3 daily doses) and lanreotide (slow release formulation, 30 mg every two weeks) were introduced in the schedule treatment, in order to improve the symptoms related to hyperinsulinemia the former and to inhibit gastrin and insulin hypersecretion the latter. A high hydration regimen plus hydrochlorothiazide 25 mg a day was also recommended in order to achieve normocalcemia. During the first three months of therapy a progressive improvement of clinical symptoms occurred resulting in a decrease of frequency and severity of hypoglycemic events. At the three month hormonal follow-up, normalization of gastrin as well as marked decrease of C-peptide with normalization of the insulin to glycemia ratio occurred. Neither gastro-intestinal side effects nor gallbladder modifications were observed at this time. Therefore, omeprazole treatment was stopped, diazoxide treatment was lowered (150 mg a day divided in 3 daily doses) and lanreotide was given at the dose of 60 mg every four weeks. Due to the progressive increase of PRL levels, a cabergoline schedule treatment was started in order to control secreting and proliferating activity of the pituitary tumor. At six month follow-up, a stable normalization of gastrin levels, a further decrease of insulin and C-peptide and a suppression of PRL levels were observed, allowing modifying the treatment by stopping diazoxide and

decreasing cabergoline doses. At this time, lanreotide Autogel 120 mg every eight weeks was also started in place of lanreotide 60 mg every four weeks. This hormonal picture remains unchanged at the twelve month follow-up in spite of the therapeutic modifications (Figure 1). From the clinical point of view, these results paralleled the complete disappearance of hypoglycemic events and gastro-intestinal disorders. A morphological evaluation of the pancreatic endocrine tumors was performed one year after the beginning of the treatment: compared to basal CT scan, the pancreatic nodules were stable in size and number. Contrast enhancement of the nodules, which was high and rapid at baseline, was then scarce after medical therapy (Figure 2).

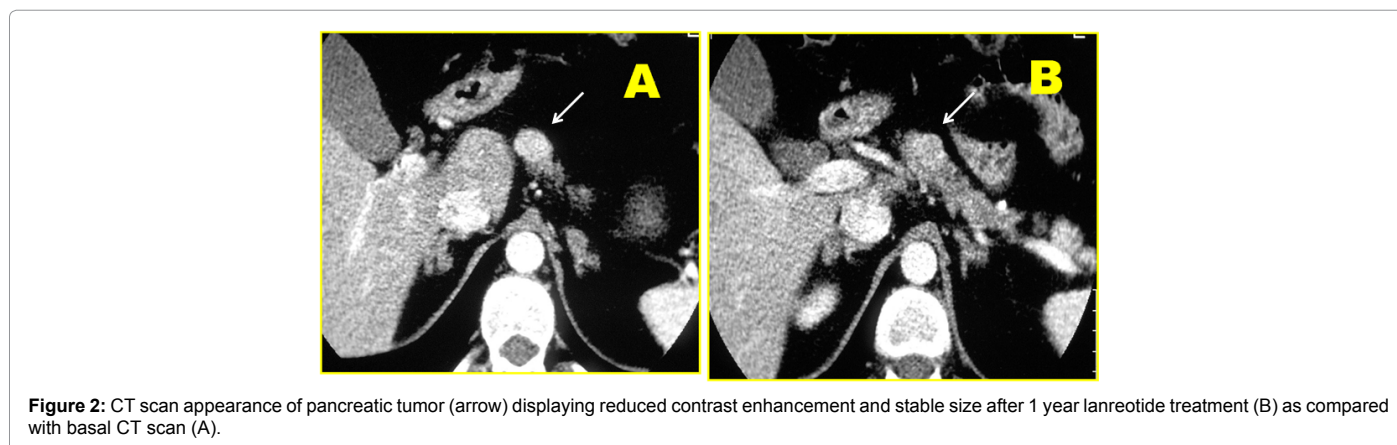
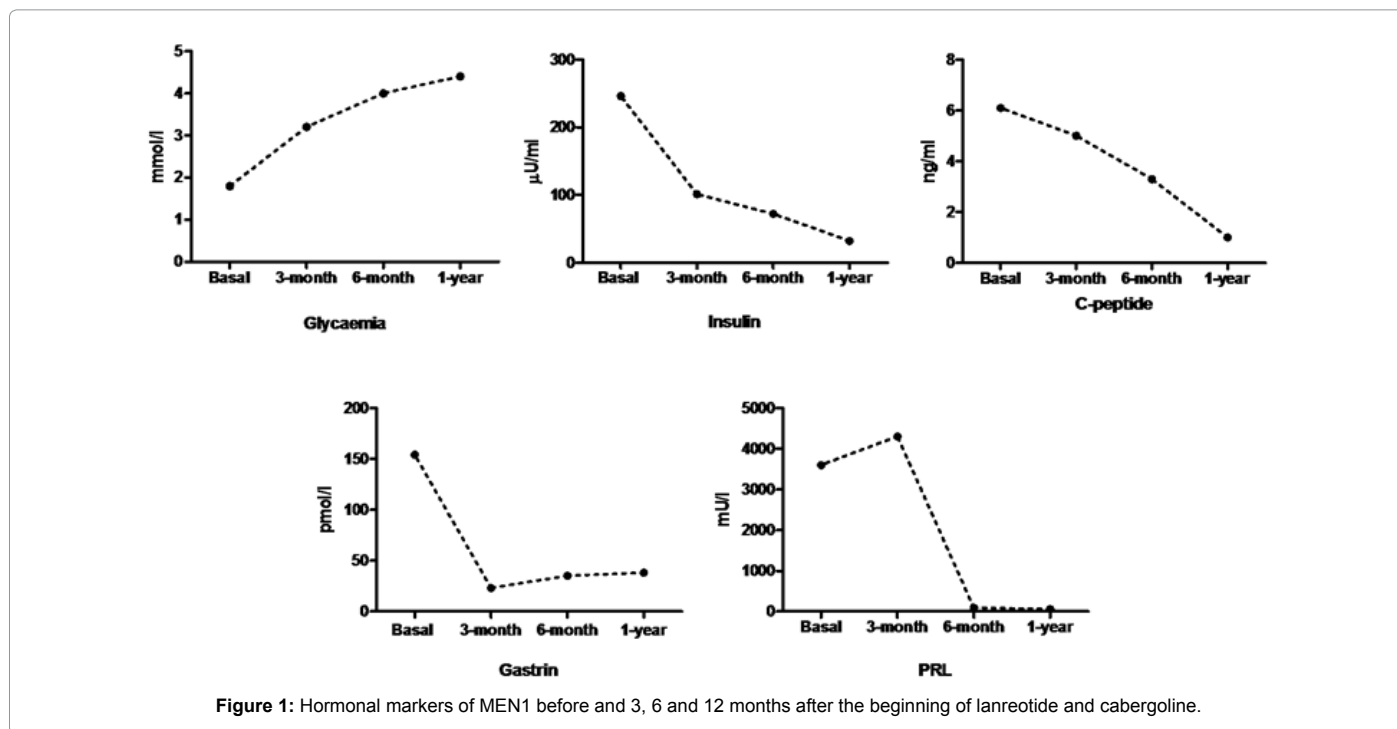
Due to the complete and stable normalization of symptomatology as well as the possibility to completely remove pancreatic tumors, the patient underwent pancreatic surgery consisting of distal pancreatectomy, tumor enucleation in the pancreatic head and duodenum and loco-regional lymph node dissection. Histology and immunohistochemistry for CGA and synaptophysin highlighted a diagnosis of well differentiated pNET (G1 NET) in a total of 16

nodules (size ranging 3-22 mm). Two insulin-positive pNETs were found in pancreatic nodules while a gastrin-positive tumor was found at the duodenal level. All lymph nodes were unaffected. A SSTRs and dopamine receptors immunohistochemical analysis was performed in one insulin-reactive tumor. The tumor specimen showed high and specific positivity for both SSTR2 and D2. Both SSTR2 and D2 strongly stained cell membrane while a weaker immunostaining was found at the cytoplasmic level (Figure 3 and 4).

After tumor resection, the patient recovered rapidly and was discharged without any therapy but cabergoline. Both basal and secretin-stimulated pancreatic hormone values were normal and neither clinical symptoms nor tumor recurrence were after a four year follow-up.

Discussion

Surgery represents the treatment of choice for MEN1-related tumors. This approach is associated with significant benefits in



terms of survival. Concerning nonfunctioning pNETs, tumors >2 cm have to be operated, while the surgical risk-benefit ratio should be carefully weighted in small tumors (<2 cm), which are generally benign. Prophylactic surgery has been proposed to remove small or radiologically unapparent tumors in order to avoid malignant transformation. However, this approach is controversial because pNETs <2 cm seem to have an indolent behavior as well as because of the high risk of surgical complications and mortality [8]. In MEN1-related insulin-secreting pNETs, the aim of surgery is to control symptoms by excising all insulin-secreting tissue but it is of great relevance in this attempt an accurate preoperative localization of the tumors [7]. Role,

type and timing of surgery for MEN1 gastrinomas is controversial not only because these tumors are usually multiple, frequently with lymph node metastases, associated with other pNETs but also because surgery (without a Whipple resection) is followed by recurrence in >90% of cases [7].

Since MEN1-related primary hyperparathyroidism affects all parathyroid tissue, surgical treatment should be a near-total or total parathyroidectomy. This strategy exposes MEN1 patients to the risk of postsurgical hypoparathyroidism and, at the same time, disease persistence or relapse occur in many cases [15].

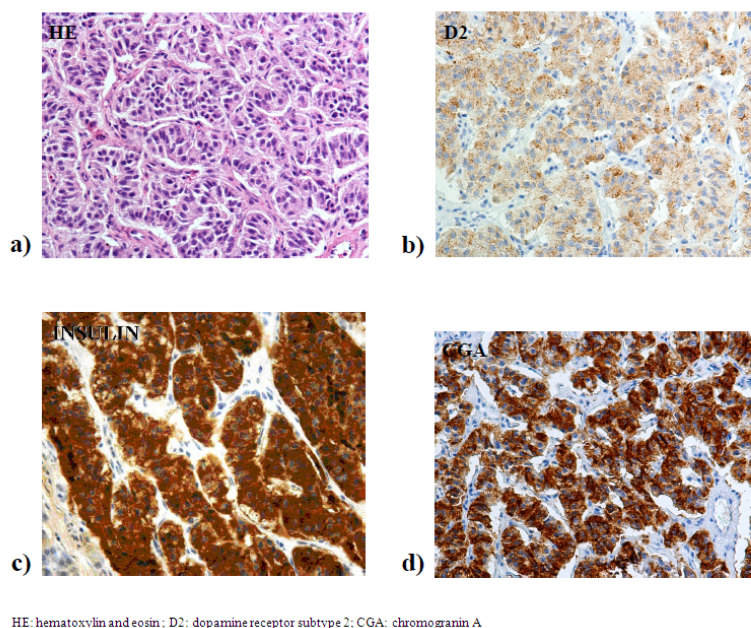


Figure 3: Histology and immunohistochemical expression of dopamine receptor subtype 2, insulin and chromogranin A (CGA) in tumor cells. a) well differentiated neuroendocrine tumor (hematoxylin and eosin, 40x magnification); b) dopamine receptor subtype 2 strongly stained cell membrane while a weaker immunostaining was found at the cytoplasmic level (40x magnification); c) insulin and d) chromogranin A strongly stained tumor cells (40x magnification).

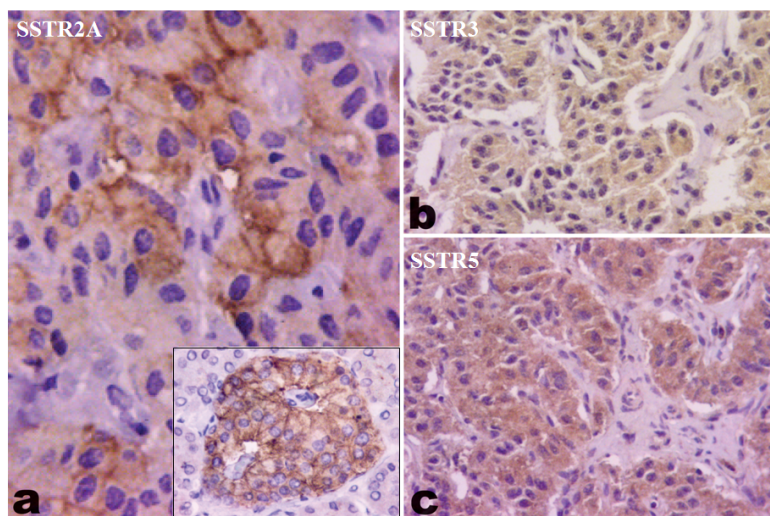


Figure 4: Immunohistochemical expression of somatostatin receptors (SSTR) in tumor cells. SSTR2A has a predominantly cell membrane staining (a), as also observed in a control pancreatic islet (a, inset). Conversely, somatostatin receptor subtypes SSTR3 (b) and SSTR5 (c) have a weak diffuse or finely granular cytoplasmic reactivity in the majority of neoplastic cells [magnification 400x (a) and 200x (b, c and insert of a)].

Treatment of pituitary tumors in MEN1 varies according to the type of adenoma and it is identical to that performed in sporadic pituitary tumors [2]. Transphenoidal adenomectomy is generally used by an endoscopic endonasal approach when possible, but MEN1 pituitary adenomas are frequently bigger than the sporadic ones at the time of diagnosis making surgery more difficult and risky.

For all these reasons, surgery is not able to obtain tumor control in the most of MEN1 patients, unless to be extremely radical and dangerous for patient life quality as well as for his life.

SSAs (octreotide and lanreotide) represent the gold standard in the treatment of acromegaly and functioning NETs [16]. Besides, the control of functioning endocrine syndromes related to NETs, the anti-tumor activity of SSAs has been demonstrated in both functioning and nonfunctioning NETs. Although an objective response rate of 10% or less has been reported, tumor stabilization occurs usually in more than half of the cases [17]. The PROMID study is a double-blind placebo-controlled prospective randomized study. It was able to demonstrate the antiproliferative efficacy of octreotide LAR in patients with metastatic NET of midgut [10]. The most favorable outcome of PROMID was the long-time stabilization of tumor growth. A significantly higher time to progression was obtained in patients with low tumor burden and hepatic involvement. SSAs seem to induce lower response rates in insulin-secreting NET than in midgut NET, either in control of hormone secretion or in suppression of proliferating activity [18]. Control of insulin secretion is often difficult due to the low expression of SSTR2 and SSTR5 in insulin-secreting pNET, which also explains the low percentage of Octreoscan-positive tumors. Moreover, the SSA-induced inhibition of contra-regulatory hormones such as glucagon, GH and IGF-1 may be higher than insulin suppression, resulting in scarce effectiveness in the improvement of hypoglycaemia [19]. Nevertheless by using the newly developed long-acting slow-release formulation SSAs, a long-time stabilization may be achieved in individual patients with insulin-secreting NETs, selected by a strongly positive Octreoscan. On the contrary, it is well known that SSAs are able to reduce serum gastrin levels and consequently gastric acid output in patients with Zollinger-Ellison syndrome. These results have been obtained both with short-term and long-term SSAs [20]. Regression of gastric carcinoids associated with MEN1 Zollinger-Ellison syndrome has been also demonstrated after treatment with long acting SSAs [21].

Therapy with SSA has been also evaluated in primary hyperparathyroidism. Although negative or inconclusive results with short-acting octreotide were published, a six-month experience with long-acting SSAs in MEN1 patients showed encouraging results with a significantly decrease in serum PTH concentrations and a clear improvement in biochemical abnormalities related to PTH excess (serum calcium, urinary calcium, serum phosphorus, renal threshold phosphate concentration) [15]. Furthermore, a positive somatostatin immunostaining was reported in parathyroid carcinoma partially responsive to SSA as well as in human parathyroid adenomas both sporadic and MEN1-related [15,22,23].

Pituitary adenomas express multiple SSTR subtypes. However, the expression of SSTR in these lesions has high variability and it may explain the variable responsiveness of different type of pituitary adenomas to medical treatment with the SSA [24]. In fact, in GH-secreting pituitary adenomas, in which both SSTR2 and SSTR5 are involved in the regulation of GH secretion, SSAs have become the cornerstone of medical treatment and are used when surgery is contra-indicated or has failed to normalize GH levels [24,25]. In prolactinomas, the low

abundance of SSTR2 explains the lack of effectiveness of octreotide in lowering the elevated PRL levels. SSAs successfully suppress TSH levels in the large majority of patients with TSH-secreting pituitary adenomas, probably due to the high level of SSTR2. Although SSTR2 are expressed by a significant proportion of nonfunctioning pituitary adenomas, SSAs seem to be ineffective in this type of patients [24].

In the current case, a MEN1 patient with pituitary hyperprolactinaemia, primary hyperparathyroidism, insulinoma and Zollinger-Ellison syndrome experienced a complete remission of all symptoms related to MEN1 tumors after combined treatment with SSA and DA. This patient presented multiple pNETs which were revealed at CT scan as hypervascular tumors with early contrast enhancement. The pNETs are commonly characterized at CT scan by the typical appearance of a hypervascular lesion [26]. Because of number, size and pancreatic spread of tumors, together with the presence of uncontrolled endocrine syndromes, abdominal surgery was not considered as first option and diazoxide treatment was started with a partial control of hypoglycaemia. However, after beginning of SSA and DA therapy, a further clinical improvement with disappearance of hypoglycemia and gastric acid hypersecretion was observed. At the same time, stabilization of the pancreatic lesions occurred as well as reduction of the contrast enhancement at CT scan, which was likely expression of decreased tumor activity [27]. To note, after surgery, the immunohistochemical analysis of tumor samples showed high and specific positivity for SSTR2 and D2 in one of the insulin-immunoreactive lesions. The presence of SSTR2 and D2 could explain the excellent clinical response concerning the insulinoma-related symptoms in this patient after beginning of treatment with lanreotide Autogel and cabergoline.

Double-staining experiments showed that D2 co-localized with insulin-containing secretory granules and quinpirole, a D2-like receptor agonist, was able to inhibit glucose-stimulated insulin secretion, suggesting a potential implication of D2 on this activity [28]. This effect has been observed *in vivo* in patients with Parkinson disease treated with L-dopa [29]. Besides, it has been demonstrated that D2 are expressed in NET associated with ectopic ACTH syndrome and that cabergoline may be effective in controlling cortisol excess in a subgroup of these patients [30]. Nevertheless, O'Toole et al. systematically quantified not only SSTR subtypes but also D2 mRNA in a large series of human NETs by PCR. SSTR1, SSTR2 and D2 resulted to be expressed in 100% of human gastroenteropancreatic NETs [31].

The well recognized expression of dopamine receptors in neuroendocrine tumors of different origin and type suggest a regulatory role for these receptors. An antisecretory activity has been clearly demonstrated in different secreting neuroendocrine tumors, while their role as antiproliferative agents has to be better investigated. Nevertheless, several molecular pathways, such as MAPK and ERK, induce anti-proliferative effects through dopamine receptor-mediated activation [32].

These findings support the combined use of SSA and DA in the treatment of gastroenteropancreatic NETs. Different studies, based on the evidence that pituitary adenomas express both SSTR and D2, had shown how the combined therapy with SSA and DA is an effective and well-tolerated medical approach for patients with secreting (particularly in GH-secreting adenomas) and clinically non-functioning pituitary adenomas (in which, on the contrary, the response rate to SSA and DA alone is limited) [33-35]. Finally, SSTR/D2 chimeric molecules have been demonstrated to display greatly enhanced potency and efficacy, as compared with that of individual SSTR or D2 receptor agonists. *In vitro* studies with functioning pituitary adenoma cells have demonstrated

that the chimeras have exceptional activity with regard to suppression of GH, prolactin and ACTH secretion as well as antiproliferative activity [36].

From our knowledge, there are no experiences on the combined use of SSA and DA in primary hyperparathyroidism but it has been demonstrated the expression of D2 as well as SSTR in parathyroid glands [15,37].

In conclusions, a combined therapy with SSA and DA was associated with complete normalization of hyperinsulinemic hypoglycaemia syndrome, Zollinger-Ellison syndrome, primary hyperparathyroidism, prolactinoma in a patient with MEN1. In this attempt, a synergistic effect of lanreotide and cabergoline is suggested by the high expression of both SSTR and D2 receptors. Besides, in MEN1 patients, SSA and DA should be taken in account not only to normalize the functional syndromes but also to induce antiproliferative effects.

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