

SOMATOSTATINOMA

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ABSTRACT

Somatostatin-secreting tumors, or somatostatinomas represent less than 1% of functioning gastrointestinal neuroendocrine neoplasms (NENs) and their estimated incidence is about 1 in 40 million individuals per year. The spectrum of the somatostatinoma syndrome consists of diabetes mellitus, diarrhea/steatorrhea, cholelithiasis, hypochlorhydria, and weight loss. Tumors that demonstrate D-cell differentiation based on immunohistochemical labelling with somatostatin but lack symptoms of somatostatinoma syndrome, such as those observed within the ampulla and duodenum, should be designated as somatostatin-producing well-differentiated NENs and are not considered somatostatinomas. Hereditary pancreatic somatostatin-producing well-differentiated NENs can be found as part of multiple neuroendocrine neoplasia type 1 (MEN1) and von-Hippel Lindau (VHL) syndrome, whereas duodenal (peri-ampullary somatostatin-producing NENs can be found in patients with neurofibromatosis type 1 (NF1). The polycythemia-paraganglioma-somatostatinoma syndrome is a rare syndrome including multiple paragangliomas, duodenal somatostatin-producing NENs (exclusively found at the ampulla of Vater) associated with high erythropoietin (polycythemia) underlying paraganglioma/pheochromocytoma. The diagnosis of a somatostatinoma requires measuring fasting plasma somatostatin hormone concentration. A 3-phase CT, MRI, positron emission tomography (PET)-CT with gallium-labelled somatostatin analogs, or endoscopic ultrasound (EUS) should be performed for the precise localization of somatostatinomas in the pancreas or duodenum. A biopsy or surgical resection is required for grading (Ki67 index)

and immunohistochemistry for somatostatin expression on tumor samples. Management of somatostatinomas includes medical treatment of the excess somatostatin production, surgical and/or radiological interventions, peptide receptor radiotherapy and targeted or cytotoxic therapies.

INTRODUCTION

The tetradecapeptide somatostatin is the main peptide released from somatostatinomas. This hormone was successfully isolated in 1973 by Paul Brazeau and colleagues in the research group of the French-US endocrinologist and Nobel prize laureate Roger Guillemin (1). Somatostatin inhibits numerous endocrine and exocrine secretory functions. Almost all gut hormones are inhibited by somatostatin, including insulin, glucagon, gastrin, secretin, and gastric inhibitory polypeptide (GIP). In addition to inhibition of the endocrine secretions, somatostatin has direct effects on a number of other target organs. For example, it is an inhibitor of gastric acid and pancreatic enzyme secretion, it has marked effects on gastrointestinal transit time, intestinal motility, and absorption of nutrients from the small intestine. In the nervous system, somatostatin acts as a neurotransmitter or neuromodulator and its roles in the fine-tuning of neuronal activity and involvement in synaptic plasticity and memory formation are now widely recognized (2).

In 1977, the groups of the Danish physician Lars-Inge Larsson and that of the US physician Om P. Ganda independently reported the first two cases of pancreatic somatostatinoma (3, 4). In 1979, a full description of the somatostatinoma syndrome caused by a periampullary

neuroendocrine tumor was reported by the Austrian gastroenterologist Günter Krejs and colleagues (5, 6). Since then, numerous cases have been reported until present, most of them being sporadic, but some of them now being recognized as part of classic or emerging genetic syndromes.

Somatostatinomas are very rare neuroendocrine neoplasms (NENs); their estimated incidence is about 1 in 40 million individuals per year in the general population and they account for less than 1% of functioning pancreatic neuroendocrine neoplasms (PanNENs). These panNENs can arise throughout the pancreas, but approximately two thirds involve the head of this organ (7). The mean patient age at diagnosis is 55 years and these tumors occur more commonly in females (7-9).

CLINICAL PRESENTATION

Although somatostatinomas secrete somatostatin, clinical presentations related to high somatostatin levels are found in less than 5% of cases. This may depend on the location of the NEN (generally pancreatic), as well as intermittent somatostatin secretion from the NEN (3, 9). The spectrum of the somatostatinoma syndrome consists of diabetes mellitus, diarrhea/steatorrhea, cholelithiasis, hypochlorhydria, and weight loss. This implies that the majority of somatostatinomas do not present with the typical somatostatinoma symptoms, but are silent. Tumors that demonstrate D-cell differentiation based on immunohistochemical labelling with somatostatin but lack symptoms of somatostatinoma syndrome, such as those observed within the ampulla and duodenum, should be designated as somatostatin-producing well-differentiated NENs and are not considered somatostatinomas. Patients harboring these tumors experience symptoms related to the tumor mass effect, their metastases, or the invasion of contiguous structures. Therefore, these silent NENs are generally detected by Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or, on occasion, by Somatostatin Receptor Imaging (SRI) and Endoscopic Ultrasonography (EUS). The most common symptom for all somatostatin-producing well-differentiated NENs is abdominal pain, occurring in over 50% of patients. Duodenal tumors can also present with jaundice and gastrointestinal bleeding (9-11).

Secretion of different hormones by the same panNEN, sometimes resulting in two, or more synchronous, or metachronous distinct endocrine syndromes, is now being recognized with increasing frequency. However, second, or metachronous somatostatin secretion has thus far not been recognized. These possibilities should be considered during endocrine work-up and follow-up of patients with panNENs (12, 13).

Somatostatin has been found in many tissues outside the GI tract. Prominent among those are the hypothalamic and extrahypothalamic regions of the brain, the peripheral nervous system (including the sympathetic adrenergic ganglia), and the C cells of the thyroid gland. Therefore, high plasma concentrations of somatostatin have been found in tumors originating from these tissues (14). Pheochromocytomas and paragangliomas are other examples of neuroendocrine tumors that produce and secrete somatostatin in addition to other hormonally active substances (15). However, these tumors do not present with signs or symptoms of the somatostatinoma syndrome.

HEREDITARY TUMORS

Hereditary pancreatic somatostatin-producing NENs can be found as part of multiple neuroendocrine neoplasia type 1 (MEN1) and von-Hippel Lindau (VHL) syndrome, whereas duodenal, peri-ampullary, somatostatin-producing NENs can be found in patients with neurofibromatosis type 1 (NF1) (16-20). An overview of the MEN1 syndrome is provided in the chapter "MEN1". Previously known as Von Recklinghausen disease, NF1, the most frequent neurocutaneous syndrome, is an autosomal dominant condition. The reported incidence is 1/2500-1/3000 (39,40). The mutation causing the condition is at the level of NF1 gene (on chromosome 17) which induces a malfunction of the RAS/MAPK pathway. The presence of a duodenal somatostatin-producing NEN has a higher risk in NF1 patients than in the general population, but this is not the most prevalent tumor encountered in these patients. Some studies report on the combined diagnosis of GIST and somatostatin-producing NENs in subjects with neurofibromatosis type 1 (9-11, 21-25).

The polycythemia-paraganglioma-somatostatinoma syndrome (also called Pacak-Zhuang syndrome) is a rare new syndrome including multiple paragangliomas, duodenal somatostatin-producing NENs, which are

exclusively found in the region of the ampulla of Vater, and a high circulating erythropoietin concentration resulting in polycythemia. A gain of function involving the mutation of Endothelial PAS domain-containing protein 1 [EPAS1, also known as hypoxia-inducible factor-2alpha (HIF-2alpha)] gene underlies the Pacak-Zhuang syndrome. Moreover, non-mosaicism somatic mutations of HIF-2alpha seem to induce the same syndrome but with late onset. A somatic gain-of-function HIF-2alpha mutation results in the stabilization of HIF-2 α , which is known to upregulate the erythropoietin gene accounting for polycythemia in these patients (25-33).

However, while the association of somatostatinomas / somatostatin-producing NENs with these inherited disorders is intriguing, a link between the known gene mutations of these disorders with the development of somatostatin-producing NENs has not been clearly established.

DIAGNOSIS

The diagnosis of somatostatinoma requires the combination of typical clinical signs and symptoms with measuring the fasting plasma somatostatin hormone concentration, which should be at least 3 times over the upper reference value (> 25 pmol/L (> 60 pg/mL). In case

of an indeterminate test result, stimulatory examinations such as secretin or calcium stimulation tests can be used, but these tests lack standardization. Anatomic and functional imaging modalities are important in the localization of a somatostatinoma. As in other NENs, 3-phase CT, MRI, or endoscopic ultrasound (EUS) should be performed for the precise localization of these tumors in the pancreas or duodenum. To detect distant metastases, somatostatin receptor imaging should be used as somatostatinomas express high numbers of different somatostatin receptor subtypes. Currently, positron emission tomography (PET)-CT with ⁶⁸Ga-labelled somatostatin analogs (DOTATATE, DOTANOC, DOTATOC) has the highest sensitivity for detecting metastases of grade 1-3 panNENs (34, 35). In line with the work-up for all NENs, a biopsy is advised to confirm the diagnosis and for grading (Ki67 index), as the grade can influence treatment selection. An overview of the current staging and grading systems is provided in the chapter “Insulinoma” (36). Generally, though, pathological examination and immunohistochemistry for somatostatin expression on tumor samples after surgery or biopsy confirms the definitive diagnosis. The tumor further shows diffuse positivity for keratins, INSM1 and synaptophysin and is less consistently positive or negative for chromogranin A (7, 9, 35, 37), see Figure 1.

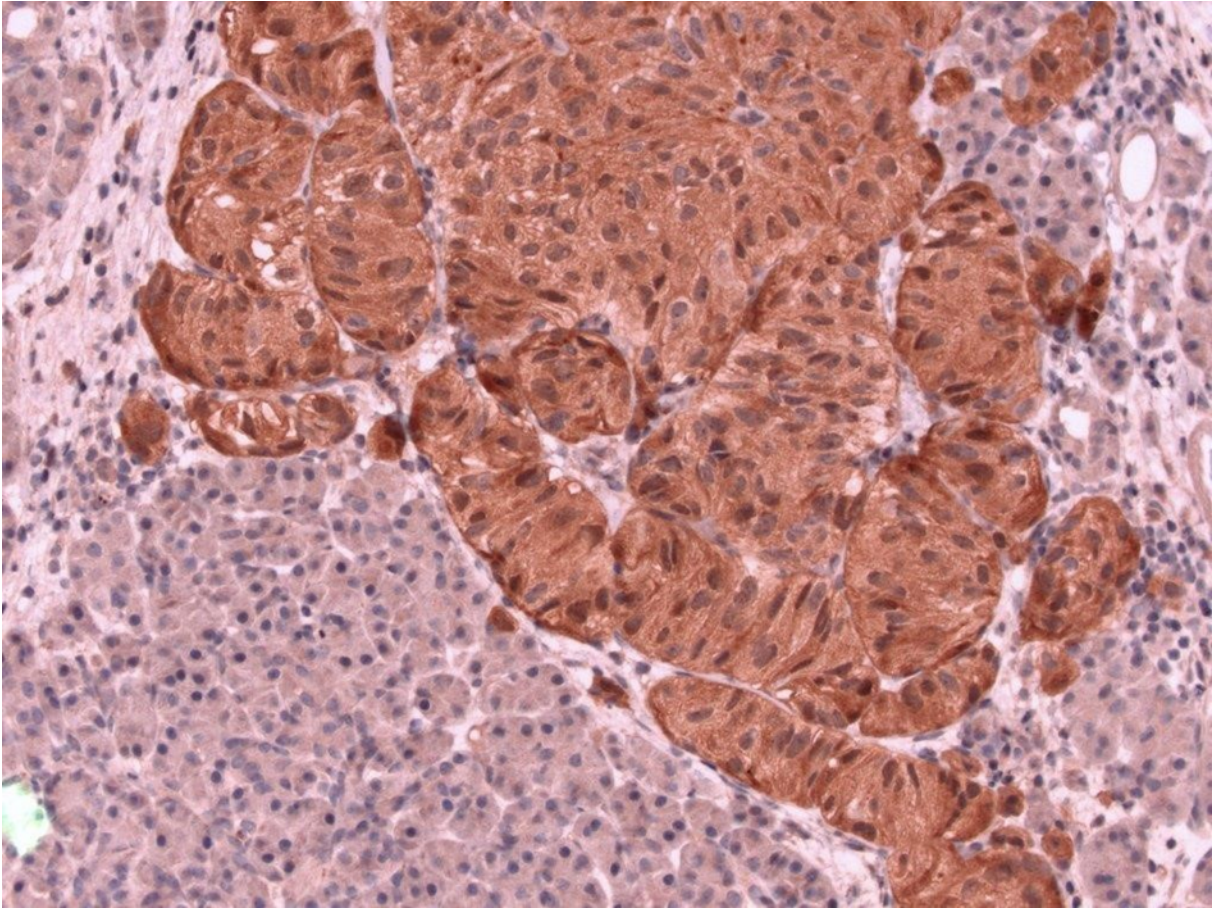


Figure 1. A malignant metastasizing pancreatic endocrine tumor located in the tail of the pancreas with positive immunohistochemical staining of somatostatin (Courtesy of Günther Klöppel).

TREATMENT

The management of somatostatinomas includes medical treatment of the excess somatostatin production, surgical and/or radiological interventions, and cytotoxic therapies when needed (35).

Curative Surgery

As for all panNENs, surgery is the only curative treatment. In the occasional patient in whom a somatostatinoma is discovered while the tumor is locoregionally confined, pancreatic or duodenal surgery should be performed to remove the somatostatinoma. In selected patients with limited liver metastases an extended surgical resection can be considered (38).

Liver-Directed Therapy

Liver metastases can be resected or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on local availability (39, 40).

Unresectable Disease

In case of unresectable metastases, treatment is focused on tumor stabilization and symptom reduction by decreasing the secretion of somatostatin. In general, anti-tumor therapy is similar to non-functioning panNENs as

specific data for somatostatinoma are often lacking. The guidelines by ENETS, NANETS and ESMO describe the selection and sequencing of somatostatin analogs, targeted therapy, ¹⁷⁷Lu-DOTATATE and cytotoxic chemotherapy (41-44).

SOMATOSTATIN ANALOGS

Somatostatin analogs became an important treatment option for patients with metastatic or inoperable NENs. First, these analogs provide relief of symptoms in patients with NENs that secrete different peptides causing various clinical symptoms and signs, especially diarrhea and weight loss in somatostatinoma patients (45). Somatostatin analogs are the first-line palliative treatment of choice to control somatostatin secretion and tumor growth. In a randomized controlled trial (CLARINET), including grade 1-2 pancreatic neuroendocrine tumors (NETs - panNETs), lanreotide autogel 120 mg every 4 weeks deep sc was associated with significantly prolonged median progression-free survival (PFS) of 38 months versus 18 months for placebo (46).

BELZUTIFAN

In the polycythemia-paraganglioma-somatostatinoma syndrome (Pacak-Zhuang syndrome) treatment with the HIF-2α inhibitor Belzutifan resulted in a reduction/normalization of the pathologically elevated levels of normetanephrine, Chromogranin A, Hemoglobin and Erythropoietin (47). Up to present no effects of this drug have been described on the somatostatin-producing NETs in these patients. Belzutifan is also used for the treatment of tumors in patients with the VHL syndrome (48, 49).

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

The expression of somatostatin receptor subtypes provides an opportunity to utilize peptide receptor radionuclide therapy (PRRT) for the treatment of metastatic somatostatinomas. PRRT with ¹⁷⁷Lu-DOTATATE has been approved for the treatment of grade 1-2 panNETs. In general, the response rate for grade 1-2 panNETs is the highest of all NETs (55%), with a median progression-free survival (PFS) of 30 months and median

overall survival (OS) of 71 months. Sub-acute toxicity mainly includes nausea, vomiting, and criteria for adverse events (CTCAE) grade 3/4 toxicity of hematologic parameters (10%). In 70% of patients with toxicity, the hematologic parameters normalize but 1% of patients treated with PRRT develops acute leukemia, and 2% myelodysplastic syndrome (50). In patients with uncontrollable hypersecretion by hormone-producing panNENs, PRRT with ¹⁷⁷Lu-DOTATATE can result in amelioration of the hormonal syndrome (51). However, data of PRRT with ¹⁷⁷Lu-DOTATATE for the treatment of metastatic somatostatinoma are not available yet.

EVEROLIMUS

Everolimus is an oral drug which inhibits mammalian target of rapamycin (mTOR) signaling. In the RADIANT-3 trial, everolimus 10 mg/day increased progression-free survival in grade 1-2 panNETs to 11.0 months as compared to 4.6 months with placebo. Also, overall survival did increase from 37.6 to 44 months. In this study 24% of patients had a functioning grade 1-2 panNET including somatostatinoma (52). As everolimus can also worsen diabetes mellitus by reducing insulin secretion from the pancreas and inducing insulin resistance, its contribution to the treatment of somatostatinoma patients is still unclear.

SUNITINIB

Sunitinib is currently one of the other options for treatment of grade 1-2 panNETs which progress during treatment with a first generation long-acting somatostatin analog. In the SU011248 trial sunitinib 37.5 mg/day increased progression-free survival to 11.4 months in comparison to 5.5 months with placebo in patients with predominantly grade 1-2 panNETs. Overall survival also increased from 29.1 to 38.6 months. In this trial, only one patient with a somatostatinoma was included in the treatment arm (53, 54).

CHEMOTHERAPY

Chemotherapy is also effective for the treatment of panNEN but no specific data for somatostatinoma are available (42, 55, 56).

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