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Review

Somatostatinoma syndrome

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SUMMARY

Somatostatinomas are extremely rare functioning endocrine tumors of the gastrointestinal tract, occurring with almost equal frequency in the pancreas (mainly in the head) and duodenum (periampullary region). The latter are often associated with von Recklinghausen disease (50%). They occur sporadically (93.1%) or as part of multiple endocrine neoplasia type 1 (6.9%). The tumors are relatively large (with an average size of 5 cm for those of pancreatic and 2.5 cm for those of duodenal origin) and usually malignant (64.7%) with metastases mainly to the lymph nodes (31.2%) and liver (27.7%). Duodenal somatostatinomas are characterized by the frequent presence of psammoma bodies. Clinical manifestations are characterized by two distinct entities, one due to somatostatin hypersecretion (inhibitory syndrome) and the other due to tumor location and growth. The inhibitory syndrome includes diabetes mellitus or glucose intolerance, cholelithiasis, weight loss, diarrhea with or without steatorrhea, and hypochlorhydria or complete achlorhydria. Clinical manifestations due to tumor location and growth include mainly obstructive jaundice, duodenal obstruction, weight loss, and gastrointestinal bleeding. Mixed clinical manifestations may occur in cases of multiple hormone secretion by the tumor (e.g. Cushing's syndrome, peptic ulcer etc.). The diagnosis is usually accidental at the time of laparotomy for cholecystectomy or during gastrointestinal imaging studies for various nonspecific complaints. For the definitive diagnosis of "somatostatinoma" histology with immunocytochemistry is mandatory. The localization of tumor or metastases may be made by imaging methods, mainly by endoscopic U/S (87.2%), and angiography (82.1%) or by surgical exploration. Treatment of choice is the surgical removal of tumor and, when possible, of metastases, with or without adjuvant chemotherapy. Due to their slow natural course, somatostatinomas have a better prognosis than pancreatic or biliary duct cancer.

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INTRODUCTION

The somatostatinoma syndrome is a distinct clinical entity that can be clearly differentiated from those of the other neuroendocrine tumors. Tumors (termed as somatostatinomas) are the least common among neuroendocrine tumors and are located primarily in the pancreas and duodenum (Table 1). Some of the clinical manifestations and biochemical findings reflect the excess of somatostatin secretion. It is noteworthy that most duodenal somatostatinomas were simultaneously diagnosed as "carcinoid somatostatinomas" or "somatostatin-secreting carcinoids"[1] and may also be classified as foregut carcinoids.[2] In fact there is considerable confusion surrounding the term "somatostatinoma" as well as the histologic classification and the spectrum of clinical findings.

HISTORICAL VIEW

In 1977 Ganda et al,[3] and Larsson et al[4] independently reported the first two cases of somatostatinoma, while the full biochemical, morphologic and clinical syndrome was characterized by Krejs et al[5] in 1979. The case of Ganda et al, a 46-year-old woman, had a well established diagnosis of diabetes mellitus of eight year duration and a pancreatic mass fortuitously visualized during cholecystectomy for cholelithiasis. The initial impression was that she had a "non functioning" islet-cell tumor. The tumor ultrastructure had a distinctive endocrine mor-

phology, resembling D cells, while it contained a large quantity of immunoreactive somatostatin. After complete resection of the tumor the patient became euglycemic. The case of Larsson et al was a 55-year-old woman with diarrhea and steatorrhea, abdominal pains of long duration, hypochlorhydria and diabetic glucose tolerance. During cholocystectomy, as in the case of Ganda et al, a tumor located in the head of the pancreas with liver metastases was detected. Examination of biopsy specimens showed the tumor to be of endocrine type and cells were indistinguishable from islet D cells. Radioimmunoassay of blood-samples obtained by tumor vein catheterization revealed very high levels of somatostatin immunoreactivity, while tumor extracts inhibited insulin and glucagon secretion from isolated perfused porcine pancreas. Another case, published by Kowacs et al[6] in the same year, has been considered by certain authors as compatible with somatostatinona.[7]

EPIDEMIOLOGY

Incidence

Somatostatinomas are extremely rare functional endocrine tumors of the gastrointestinal tract with an estimated annual incidence of 1 in 40 million.[2,8,9] They may occur either sporadically (93.1%) or rarely as part of multiple endocrine neoplasia syndrome type 1 (MEN 1) (6.9%).[1,10] They also can present in association with pheochromocytoma and neurofibromatosis type I (termed also von Recklinghausen disease), in the MEN 2 syndrome.[2,11-15] It is noteworthy that duodenal somatostatinomas are frequently (43.2-50%)[1,16] associated with von Recklinghausen disease[16-21] and rarely with von Hippel Lindau disease.[12,22] The relation between somatostatinoma and multiple endocrine neoplasia type I and multiple neoplasia type II remains unclear**.** Possibly some cases of somatostatinomas represent manifestations of mixed forms of multiple endocrine neoplasia syndromes.[23]

Gender

Both sexes appear to be affected with almost equal frequency.[1,24,25]

Age

Statistical evaluation indicated a significant difference in age only between female patients with pancreatic and duodenal somatostatinomas (55.4 years vs 48.7 years).[1] Most patients are 40 to 60 years old with a mean age of about 51-53 years.[26]

PATHOLOGY

Tumor location

Somatostatinomas are found with almost equal frequency in the pancreas (46.8%) and in other sites of the gastrointestinal tract (53.2%) mainly in the duodenum and particularly in the ampula.[17] Other sites such as the lung,[27] the liver,[28] or the kidney[29] are very rare. The head of the pancreas is the predominant (55.6%) site of somatostatinomas followed by the tail (27.2%) (Table 1).[1]

Size/Malignancy/Metastases. Somatostatinomas are usually large, ranging from 1 to 10 cm or more in diameter[1,2,30] with a mean size of 5 cm from pancreatic somatostatinomas and 2.5 cm for those of duodenal origin (Table 2).[2] In the majority of cases (>90%) the tumor is solitary.[1,2,4]

The malignant nature of the tumors varies with an average of 64.7% of cases. Extreme and constant hypersomatostatinemia is consistent with a malignant tumor associated with metastases.[5] Somatostatinomas occurring as sporadic cases have a higher rate of malignancy than those occurring as part of multiple endocrine neoplasia.[1]

The overall rate of metastases is 53% without differences between pancreatic and duodenal somatostatinomas.[1] Lymph nodes[1,31,32] and liver[1,32-37] are the most common sites of metastases with some differences in the rate between pancreatic and duodenal somatostatinomas[1] (Table 3). On the other hand, extraduodenopancreatic somatostatinomas appear to have a higher rate of metastases (89%).[1] Metastatization in duodenal somatostatinomas associated with von Recklinghausen disease is relatively rare (27%) and mainly confined to lymph nodes (88%).[16]

Tumor histology. The tumors appear as well differentiated islet cells with D-cell granules in electron microscopy.[30] Immunohistochemical analysis demonstrates somatostatin-like immunoreactive material in all tumors.[5,30]

Psammoma bodies (psammomatous calcifications) are frequently encountered in the glandular lamina of duodenal somatostatinomas (49.4-66%), whereas their presence in other neuroendocrine tumors or in pancreatic somatostatinomas is very rare (2.5%).[1,16,38] The histological finding of psammoma bodies is important in the diagnosis of duodenal somatostatinomas.[39] A review of the literature reveals that somatostatinomas with psammoma bodies are found only in the duodenum and do not produce significant amounts of peptides other than

Table 1. Location of somatostatinomas[1]

Location	No	%	Location	No	%
Pancreas	**81**	**46.8**	Head	45	55.6
			Body	6	7.4
			Tail	22	27.2
			Head/Body	1	
			Body/Tail	2	}6.2
			Diffuse/Head+Tail	2	
			Not srecified	3	
Extrapancreatic[1]	**92**	**53.2**	Duodenum	81	88.0
			Lungs	2	
			Gallbladder	1	
			Choledochus	1	
			Stomach	1	}9.8
			Jejunum	1	
			Colon	1	
			Rectum	1	
			Thyroid	1	
			Unknown	2	2.2

1: Other sites, as the lung[27], the liver[28], or kidney[29] have also been reported

Table 2. Comparative data of size in somatostatinomas[1]

Size (cm)	Pancreatic (N°=62)		Duodenal (N°=70)		Overall (N°=138)	
	No	%	No	%	No	%
< 1	4	6.5	12	17.1	18	13.0
1.1-2	5	8.1	29	41.4	35	25.4
Subtotal	**9**	**14.5**	**41**	**58.6**	**53**	**38.4**
2.1-5	29	46.5	27	38.6	59	42.8
5.1-10	22	35.5	2	2.9	24	17.9
> 10.1	2	3.2	0	0	2	1.4
Subtotal	**53**	**85.5**	**29**	**41.4**	**85**	**61.6**
Average size	**5.11 cm** (N°=57)		**2.41 cm** (N°=70)		**3.57 cm** (N°=132)	

somatostatin.[40] In general, these tumors are composed of regular cells arranged in glands or acini with psammoma bodies and can be misdiagnosed as adenocarcinomas.[41]

It is noteworthy that a low but variable proportion of somatostatin-containing cells is present in a number of neoplasms, the majority of which are derived from cells of the neuroendocrine system, such as oat cell carcinoma, carcinoid tumors (bronchial, thymic, intestinal), laryngeal neuroendocrine tumors, medullary thyroid carcinoma, retinoblastoma, ganglioneuroblastoma, glucagonoma, vipoma, gastrinoma, paraganglioma, colon carcinoma and possibly others.[42,43]

CLINICAL MANIFESTATIONS - PATHOPHYSIOLOGY

In the majority of patients, somatostatinomas are symptomatic (92.7%, Table 4). Some differences between pancreatic and duodenal somatostatinomas appear in the tables 4 and 5. Generally, two different pathogenetic categories of clinical manifestations can be distinguished.

One includes those due primarily to somatostatin hypersecretion, characterized as inhibitory syndrome and

the other those due to endocrine tumor location and growth. The inhibitory syndrome is more common in pancreatic somatostatinomas (18.5-66%) than in duodenal (1.2%).[1,16] Another category of clinical manifestations includes endocrine tumors with secretion of more than one hormone.[6,45-47]

General symptoms, such as abdominal pain, anorexia, nausea or vomiting, dyspepsia etc. are often associated with somatostatinomas independent of their origin.[1,20,26]

Inhibitory syndrome

The biologic actions of somatostatin in excess explain the "inhibitory syndrome" in somatostatinomas.[48,49] It is well known that somatostatin, originally termed somatotrophin release inhibitory factor (SRIF) is a small cyclic peptide hormone present in humans as the molecular forms SRIF-14 (consisting of 14 amino acids) and SRIF-28 (28 amino acids).[50,51] Somatostatin suppresses the release of growth hormone, thyrotropin, gastrin, VIP, cholecystokinin, secretin, gastric inhibitory polypeptide, insulin, glucagon and many others. On the other hand, exocrine secretions (pancreatic, biliary, gastric, intestinal) and gallbladder contractility are also inhibited by somatostatin.[5,42,52]

Analysis of tumor extracts demonstrated that somatostatin-28 and larger forms are predominant. This heterogeneity is thought to reflect incomplete processing of precursors.[7]

The inhibitory syndrome includes typical clinical manifestations and biochemical findings such as diabetes mellitus, cholelithiasis, diarrhea with or without steatorrhea, hypochlorhydria/achlorhydria and weight loss.[1,5]

Diabetes mellitus or glucose intolerance occurs in the

Table 3. Comparative data of metastases in somatostatinomas[1]

	Pancreatic (N°=81)		Duodenal (N°=81)		Overall (N°=173)	
	No	%	No	%	No	%
Liver	32	39.5	9	11.1	**48**	**27.7**
Lymph nodes	20	24.7	28	34.6	**54**	**31.2**
Bone	5	6.2	0	0	**7**	**4.0**
Mesentery/Omentum/Peritoneum	5	6.2	2	2.5	**7**	**4.0**
Lung	2	2.5	0	0	**5**	**2.9**
Adrenal	2	2.5	0	0	**3**	**1.7**
N° cases with metastases	**41**	**50.6**	**41**	**50.6**	**92**	**53.2**

***:** Brain metastases was also reported[44]

Table 4.[1] Clinical manifestations of somatostatinomas. Comparative data

	Pancreatic (N°=81)		Duodenal (N°=81)		Overall (N°=173)	
	No	%	No	%	No	%
Recorded	**78**	**96.3**	**75**	**92.5**	**164**	**94.8**
Symptomatic	**73**	**93.6**	**68**	**90.7**	**152**	**92.7**
Abdominal pain	30	38.5	32	42.7	66	40.2
Weight loss	25	32.1	15	20.0	42	25.6
Icterus	7	9.0	29	38.7	37	22.6
Diarrhea	18	60.0	8	10.7	30	18.3
Nausea/vomiting	15	19.2	8	10.7	27	16.5
Anemia	11	14.1	11	14.7	24	14.6
Abdominal tumor	14	17.9	2	2.7	19	11.6
Hepatomegaly	11	14.1	3	4.0	16	9.8
Hypertension	7	9.0	5	6.7	13	7.9
Asymptomatic	**5**	**6.4**	**7**	**9.3**	**12**	**7.3**

Table 5.[1] Some differerences between pancreatic and duodenal somatostatinomas

	Pancreatic	Duodenal
Inhibitory syndrome	**18.5%**	2.5%
Von Recklinghausen disease	1.2%	**43.2%**
Tumor size > 2 cm	**85.5%**	41.4%
Multisecretory activities	**33.3%**	16.3%
Presence of psammoma bodies	2.5%	**49.4%**
Average postoperative 5-year survival	75.2%	
- With metastases	59.9%	
- Without metastases	100.0%	

Table 6.[1] Clinical and laboratory findings in patients with the inhibitory syndrome

Clinical and laboratory findings	%
Diabetes mellitus	94.7
Biliary calculosis	68.4
Weight loss	68.4
Steatorrhea	47.4
Diarrhea	36.8
Hypochlorhydria/achlorhydria	26.3
Anemia	21.1

majority of patients (94.7%, Table 6). The severity is distributed along a broad spectrum from mild hyperglycemia to frank ketoacidosis.[53,54] The hyperglycemia is secondary to reduced peripheral glucose utilization due to relative insulin suppression by excess of somatostatin.[55] The cause of symptomatic hypoglycemia is less clear, but may be related to suppressed normal autoregulatory mechanisms such as glucagon and growth hormone and impaired sugar absorption.[24]

Gallbladder disease, mainly cholelithiasis, occurs in 25-68% of patients[1,2,24,30] (Table 6). It may be secondary to alterations in fat metabolism, to suppression of cholecystokinin by somatostatin, and to inhibition of biliary motility by somatostatin.[5,42,62,56]

Weight loss, ranging from 9 to 21 kg or more is very common (68.4%) in patients with pancreatic somatostatinoma[1,2,30] (Table 6).

Diarrhea and streatorrhea occur more often in patients with pancreatic than in those with duodenal tumors.[7,26,30] Diarrhea characteristically consists of three to ten, foul-smelling stools per day with 20 to 76 g/day steatorrhea.[30] The time course and severity of the diarrhea and steatorrhea parallels that of the disease in that is worsens when metastases occur and improves with successful tumor resection[1,26] (Table 6).

Hypochlorhydria occurs in most patients (26.3%) as a result of gastrin suppression and direct inhibition of gastric acid and pepsin secretion. Achlorhydria is not uncommon,[1] (Table 6).

Obstructive jaundice, abdominal pain, duodenal obstruction, weight loss and gastrointestinal bleeding are the commonest clinical manifestations in cases of duodenal somatostatinomas, especially those associated with von Recklinghausen's disease. Inhibitory syndrome is rare (2.5-3%).[1,16] Generally, duodenal somatostatinomas tend to be asymptomatic (Table 4).[1,57]

Mixed clinical syndromes

It has been pointed out that many cases of insulinoma represent mixed tumors containing glucagon and somatostatin-producing cells.[58] On the other hand, somatostatinomas may also produce several hormones, such as ACTH, calcitonin, VIP, pancreatic polypeptide, gastrin, insulin, glucagon and many others, that may affect the clinical manifestations.[35,59] The syndrome depends on the hormones produced, e.g. peptic ulcer in case gastrin is released,[45] Cushing's syndrome in case of ACTH production[6] or diarrheic syndrome caused by the combination of pancreatic insufficiency and disturbed intestinal absorption of water and electrolytes in case of calcitonin production.[46,47] In cases of duodenal somatostatinomas associated with neurofibromatosis, the clinical manifestations of the latter may be predominant. Neurofibromatosis type I is an autosomal-dominant disorder characterized by abnormalities of growth and differentiation of the nervous system and of certain other tissues.[60] The defining features include multiple cafı-au-lait spots, the presence of neurofibromas and different congenital abnormalities (abnormal bone formation and pseudoarhrosis, learning disability or frank mental retardation).[60-62] After birth, a variety of malignant tumors (optic glioma, neurofibrosarcoma in a cutaneous or internal location, pheochromocytoma, Wilms's tumor, rhabdomyosaroma, etc.) may appear.[61] The gastrointestinal manifestations in neurofibromatosis type I include especially neurofibromas but also malignant tumors in the bowel, liver and other organs.[61] A unusual but highly distinctive lesion is the association of neurofibromatosis type I with carcinoid somatostatinomas.

DIAGNOSIS

Laboratory findings other than increased levels of

somatostatin in peripheral blood are not diagnostic. The normal plasma level of somatostatin is less than 100 pg/ml. Patients with somatostatinoma usually have very high levels, often measured in nanograms per milliliter. A mean of 15.5 ng/ml (range, 0.16-107 ng/ml) has been reported.[30]

The diagnostic value of provocation tests, such as tolbutamide, calcium, secretin etc. is unproven with controversial findings,[10,30,64-68] but their application can be useful in some cases.[10,64,65,69]

In the majority of patients somatostatinomas are found accidentally at the time of laparotomy for cholecystectomy or during gastrointestinal imaging studies for various complaints, such as abdominal pain, diarrhea, increasing levels of hepatic enzymes, gastrointestinal bleeding or anemia, dyspepsia, obstructive jaundice etc.[9,18,22,26,30,31,61,65,70,71]

The presence of diabetes with coexisting cholelithiasis associated with diarrhea or/and steatorrhea must prompt a search for a possible somatostatinoma. Imaging modalities[1,10,31,32,71,72] and endoscopy of the upper gastrointestinal tract[1,18,31,73] (Table 7) can reveal an endocrine tumor in the pancreas or duodenum, while increased levels of somatostatin in the peripheral blood are consistent with somatostatinoma. Definitive diagnosis is made by microscopic and immunocytochemical studies.

TREATMENT

Surgical resection and adjuvant chemotherapy is the treatment of choice.[10,59,74,75] Excessive local spread of tumor due to delayed diagnosis often prohibits successful surgical treatment. Nevertheless, since somatostatinomas are characterized by relatively slow evolution, they offer more possibilities of radical excision than pancreatic cancer.[74]

Surgical. Distal pancreatectomy can be performed in tumors of the body or tail, but since the majority of somatostatinomas are in the pancreatic head or in the duodenum, a subtotal pancreatectomy or a Whipple's procedure may be necessary. Debulking a large metastatic liver tumor may effectively palliate symptoms, often for a prolonged period of time.[2,76] Prophylactic cholecystectomy should also be considered at the time of laparotomy.[8] Duodenal tumors are more often amenable to curative resection, although Whipple's procedure is often needed.[8]

Chemotherapy. Chemotherapy agents must be administerd as adjuvant therapy in case of metastatic disease or recurrence after operation.[24] Streptozotocin, doxorubicin, 5-fluorouracil, adriamycin or dacarbazine[10,24,76-79] are usually used. Objective clinical and humoral responses to chemotherapy for nonresectable or metastatic lesions can be expected in about 50% of patients.[77] Assessment of the efficacy of chemotherapy has been hindered by the rarity of these neoplasms. Hepatic embolization can also be used for palliation.[80] Two patients responded to octreotide.[81]

Patients with weight loss, anemia, pancreatic insufficiency or malnutrition may require symptomatic therapy. The diabetes mellitus, usually mild, can be controlled with hypoglycemic agents or low doses of insulin.[30] Exocrine pancreatic insufficiency may require administration of pancreatic extracts.[59,64]

PROGNOSIS

The course of somatostatinomas is often fatal, as a result of both the frequent metastatic spread of the tumor and difficulties in making an early diagnosis;[75] but, because of their slow natural course, characteristic of all neuroendocrine tumors, the postoperative 5-year survival in patients with metastases is 59.9% and without metastases 100% with an average of 77.2% (Table 5). This result is better than the survival of patients with pancreatic or biliary duct cancers.[24,74]

Table 7.[1] Imaging modalities for somatostatinomas

Imaging modalities	Pancreatic (n=81)		Duodenal (n=81)	
	No	Sensitivity %	No	Sensitivity %
Angiography	32/39	82.1	4/9	44.4
Ultrasonography	34/39	87.2	6/19	21.6
Computed tomography	42/56	75.0	8/18	44.4
Endoscopic retrograde pancreatography	15/21	71.4	13/16	82.3
Magnetic resonance imaging	11/12	91.7	1/2	-
Duodenoscopy	3/13	23.1	31/33	93.9

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