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Case Report:

Pancreatic somatostatinoma with obscure inhibitory syndrome and mixed pathological pattern*

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Abstract: Somatostatinoma is a very rare neuroendocrine tumor that originates from D cells and accounts for less than 1% of all gastrointestinal endocrine tumors. The duodenum is the most frequent site for this tumor, followed by the pancreas. We here describe a 46-year-old Chinese woman who developed pancreatic somatostatinoma presenting with the characteristic "inhibitory" syndrome, but the symptoms were obscure and seemingly uncorrelated. This case is also unique for its large tumor size and mixed pathological pattern. Distal pancreatectomy was performed, and the patient has remained well since operation. As the syndromes of somatostatinoma may be obscure and atypical, clinicians should review all clinical findings to obtain an accurate diagnosis. Aggressive surgery is preferred to improve the survival.

Key words: Neuroendocrine tumor, Somatostatinoma, Somatostatinoma syndrome, Pancreatic hormone-producing tumor, Pancreatectomy

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1 Introduction

Somatostatin-producing neuroendocrine tumor is a rare neoplasm usually arising in the pancreas and duodenum. Since its first description in 1977 (Larsson *et al*., 1977; Soga and Yakuwa, 1999), fewer than 200 cases have been reported in the literature (Marakis *et al*., 2005), with the prevalence estimated to be only one in 40 million. The tumor is characterized by positive immunochemical staining for somatostatin (Sakazaki *et al*., 1983). Early detection of pancreatic somatostatinoma is difficult due to its rarity and the variable nonspecific clinical presentations. Only a few patients present with typical somatostatinoma syndrome, including diabetes mellitus, steatorrhea, and cholelithiasis (Konomi *et al*., 1990; Anene *et al*., 1995).

In the present study, we describe a case of pancreatic somatostatinoma presenting with complete somatostatinoma syndrome. The available English literature on this tumor type is reviewed.

2 Case report

A 46-year-old Chinese woman was admitted to our hospital with recurrent upper abdominal pain for one year. The patient also had had nausea, anorexia, repeated diarrhea, and weight loss for several months. She had a history of cholecystectomy for cholecystolithiasis one year ago and twice thyroid adenoma resection, but no history of diabetes or gastric ulcer. On admission, no abnormality on physical examination was noted except for multiple thyroid nodules. Computed tomography (CT) indicated an isodense mass of 8.4 cm×3.7 cm in the body and tail of the pancreas with notable enhancement (Figs. 1a–1c). On magnetic

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resonance imaging (MRI), the tumor displayed a slightly low signal intensity on T1-weighted images and high signal intensity on T2-weighted images compared with normal pancreatic parenchyma (Figs. 1d and 1e). Ultrasonography of the thyroid revealed bilateral multiple nodules. Carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), blood glucose, calcium and amylase levels were within normal ranges. The high plasma glucose level of 2 h post glucose-load (10 mmol/L at 2 h; reference, ≤7.8 mmol/L) indicated an impaired glucose tolerance. A series of endocrine hormones, including thyroid hormones (T3, T4), human thyroid stimulating hormone (h-TSH), follicle-stimulating hormone (FSH), luteotrophic hormone, estrogen, proestrogen, prolactin, adrenocorticotrophic hormone (ACTH), cortisone, insulin, C-peptide, calcitonin, and vanillylmandelic acid (VMA), were further tested to exclude the diagnosis of type I multiple endocrine neoplasia (MEN-1). There was no abnormal finding except for elevated calcitonin (2.0 ng/ml; reference, <0.5 ng/ml). No morphologic abnormalities of the pituitary, parathyroids, or adrenal gland were found by either cranial MRI or cervical/abdominal ultrasonography.

No liver metastasis or peritoneal dissemination was identified by laparotomy, but a huge solid, non-capsulated mass, measuring about 10 cm×4 cm, was found in the body and tail of the pancreas associated with surrounding dilated vessels. Distal pancreatectomy was performed to find that the cut surface of the resected specimen was grayish-white. The diagnosis of pancreatic somatostatinoma was made by pathological examination. Microscopically, the tumor cells arranged with a mixed solid nest and trabecular pattern (Figs. 2a and 2b), and the invasion of surrounding vessels was observed but without lymph nodes involvement. The neoplastic cells were immunoreactive for somatostatin and synaptophysin (Figs. 2c and 2d), as well as CA19-9, chromogranin A (CgA), and Ki-67 (index >2%), but negative for insulin, gastrin, prolactin and P53.

The postoperative course was uneventful. The patient received no further treatment and remained healthy to date without tumor recurrence.

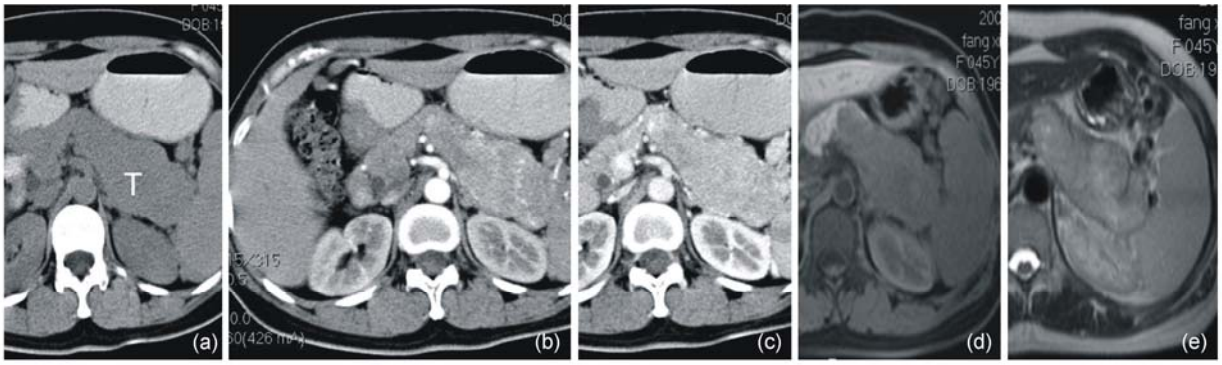

Fig. 1 (a) Computed tomography showed an isodense mass in the body and tail of the pancreas, 8.4 cm×3.7 cm in size (T: tumor); (b) In the arterial phase, the mass was notably enhanced earlier than normal pancreatic tissue; (c) In the portal-venous phase, the tumor remained enhancement; Magnetic resonance imaging revealed that the mass displayed a slightly low signal intensity on T1-weighted images (d) and high signal intensity on T2-weighted images (e)

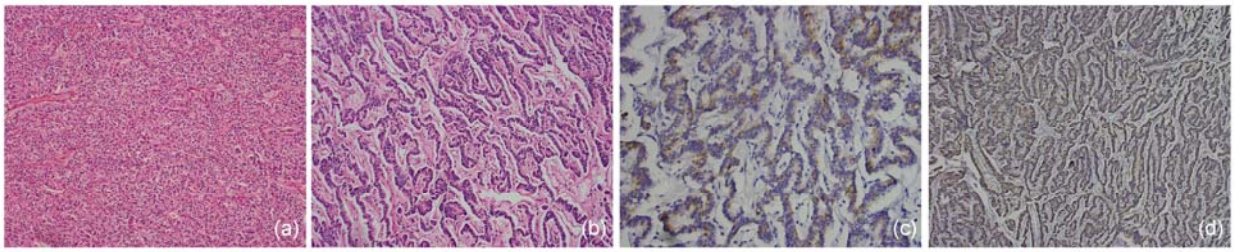

Fig. 2 Relatively homogenous neoplastic cells displayed the solid diffuse medullary arrangement (a), while in other parts, these uniform cuboidal cells showed a trabecular or glandular structure (b); (c) Most cells were immunoreactive for somatostatin; (d) Diffusely positive immunostaining for synaptophysin

(a) & (b) Hematoxylin and eosin; (c) & (d) Immunohistochemical stain. Original magnification: (a), (b) & (d) ×100; (c) ×200

3 Discussion

Pancreatic somatostatin-producing endocrine tumor is one of the rarest neoplasms, which originates from D cells and is characterized by the somatostatinoma syndrome, caused by the predominantly inhibitory actions of somatostatin on other hormones (Mozell *et al*., 1990; Moayedoddin *et al*., 2006). Additional symptoms, such as dyspepsia, weight loss, anemia, and hypochlorhydria, may also exist. Our patient presented with upper abdominal pain, weight loss, iterative diarrhea, and impaired glucose tolerance and had a history of cholecystolithiasis, which could be regarded as typical somatostatinoma syndrome. However, these seemingly unassociated and obscure symptoms did not attract our much attention to take these observations together in the diagnostic process, and the diagnosis of pancreatic somatostatinoma was not taken into consideration.

The review articles published recently are listed in Table 1 and the largest review work was carried out by Soga and Yakuwa (1999), including 81 patients with pancreatic somatostatinoma reported before 1999. We further performed a comprehensive review of 15 available reports between 2000 and 2009, and identified another 23 patients with this rare tumor. The clinical findings about these patients were summarized in Table 2. There were 56 women and 48 men (1.17:1), and the mean age was 53.0 years, ranging from 22 to 84 years. Most patients were symptomatic (94.2%), but a few patients presented with complete somatostatinoma syndrome. Most patients displayed hyperglycemia due to the inhibitory effect of somatostatin on insulin, whereas in a small portion of patients, hypoglycemia might be the complaint (Cao *et al*., 2009). With respect to the tumor location, most of these tumors arose in the head of the pancreas, followed by the body and tail. A diffuse distribution throughout the pancreas or arising from the ectopic pancreas was rarely observed (Barahona-Garrido *et al*., 2009). In some reports, pancreatic somatostatinoma was detected in association with neurofibromatosis type 1, MEN-1, and von Hippel-Lindau syndromes (Maki *et al*., 1995; Levy-Bohbot *et al*., 2004; Barahona-Garrido *et al*., 2009). Recently, some clinicians presumed that there might exist an association between gastrointestinal stromal tumors (GIST) and somatostatinoma (Barahona-Garrido *et al*., 2009).

As shown in Table 1, the majority of patients displayed a high level of somatostatin, which is helpful for an accurate diagnosis. However, a laboratory test for serum somatostatin level is often ignored when patients displayed nonspecific symptoms. Usually, somatostatinoma would appear as an iso- or low-density mass on CT images, and contrast enhancement is obvious due to hypervascularity. On MRI, the tumor displays low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (Tjon *et al*., 1994). Somatostatin receptor scintigraphy and positron emission tomography (PET) (Suzuki *et al*., 2008) are recently utilized for detecting and staging somatostatinoma. Cytological and immunochemical detection sampled by the endoscopic ultrasound (EUS)-guided fine needle aspiration can be used for preoperative diagnosis (Stelow *et al*., 2005).

Pathologically, the tumor cells arrange in a trabecular pattern including ribbon-like, gyriform and

Table 1 List of published review articles about somatostatin-producing pancreatic endocrine tumor or pancreatic somatostatinoma

Case, *n*	Sex[a]	Age[b] (year)	Symptom (%)			Tumor location (%)				HS (%)	Malignancy (%)	LM (%)	LNM (%)	Surgery (%)	Prognosis (%)[#]	Ref.
			S1	S2	S3	L1	L2	L3	L4							
27	18/9	52.6 (30–84)	77.8	63.0	40.7	51.8	7.4	18.5	7.4	66.7	85.2	70.4	29.6	NA	NA	[1]
23	13/10	53.9 (30–84)	65.2	43.5	52.2	56.5	8.7	30.4	4.3	93.7 (15/16)	73.9	69.6	34.8	82.6	56.5 (13/23)	[2]
81	45/36	55.3 (30–84)	NA	NA	60.0	55.6	27.2	7.4	9.8	NA	70.4	39.5	24.7	69.1	NA	[3]
23	11/12	44.8 (22–72)	26.1	26.1	39.1	57.1[*]	23.8	14.3	4.8	83.3 (5/6)	73.9	43.5	60.9	87.0	61.1 (11/18)	[4]

[a]: Female/Male; [b]: Age at admission. Values are expressed as median (range); S1: diabetes mellitus; S2: cholelithiasis; S3: diarrhea/steatorrhea; L1: head; L2: body; L3: tail; L4: diffuse/ectopic; HS: high somatostatin; LM: liver metastasis; LNM: LN metastasis; NA: not available; Ref.: [1] Vinik *et al*., 1987; [2] Konomi *et al*., 1990; [3] Soga and Yakuwa, 1999; [4] Present review; [#]: Alive percentage determined from the records of respective references; [*]: Twenty-one cases with tumor location information available

Table 2 Clinical characteristics of 104 patients with pancreatic somatostatinoma

Clinical data	Results
Gender	
Female	53.8% (56/104)
Male	46.2% (48/104)
Age (year)	
Mean (range)	53.0 (22–84)
Tumor location	
Head	55.9% (57/102)
Body and/or tail	35.3% (36/102)
Diffuse/ectopic	8.8% (9/102)
Symptomatic	94.2% (98/104)
Malignancy	71.2% (74/104)
Liver metastasis	40.4% (42/104)
Surgery	73.1% (76/104)

glandular structures, or a solid medullary pattern. Our patient displayed a mixed pathological pattern, consisting of both solid medullary and gyriform structures, which is relatively a rare situation. Psammoma bodies are commonly observed in duodenum somatostatinoma, but rarely in the pancreas (House *et al*., 2002). The accurate diagnosis of somatostatinoma depends on the intense positive immunochemical staining for somatostatin.

As demonstrated in Tables 1 and 2, most somatostatinomas are malignant (71.2%), with the liver, peripancreatic lymph nodes, and bone being the common metastatic sites (Tomono *et al*., 2003; Marakis *et al*., 2005). There is a unique staging system for pancreatic endocrine tumors including two major categories: well-differentiated endocrine tumors, with benign or low-malignant behavior, and poorly differentiated carcinomas that behave in a highly malignant fashion. The case presented here may be classified as "borderline tumor with uncertain behavior" according to the following clinicopathologic features: well differentiated, confined to the pancreas, >3 cm in size, angioinvasion, >2% Ki-67-positive cells/10 high power field (hpf) (Klöppel *et al*., 2004). It should be noted that, for this tumor type, malignancy is not determined by histology but the discovery of metastasis (Marakis *et al*., 2005).

Aggressive surgical is preferred for this tumor type. However, the therapeutic procedure for hepatic metastases is controversial. It is generally considered that metastatic lesions should be resected simultaneously, such as hepatic wedge resection, provided it can be done. Palliative therapies, such as lipiodol-transcatheter arterial embolization of the liver, might be effective for those with unresectable liver metastases (Sato *et al*., 2000). Liver transplantation is an alternative option but should be under careful estimation (Zhang *et al*., 2008). Little experience with chemotherapy and radiotherapy has been accumulated. Therapy with octreotide and interferon-α (IFN-α) has been shown to be beneficial in the treatment of the clinical symptoms of functional somatostatinoma (Janson, 2005; Nesi *et al*., 2008).

The prognosis of somatostatinoma is promising if the tumor is completely resected (Marakis *et al*., 2005). However, patients with unresectable metastases have a poor outcome. Close follow-up is important since the tumor is prone to local recurrence. Surveillance of serum somatostatin level is very useful and elevated levels of this hormone may indicate tumor recurrence.

4 Conclusion

In summary, pancreatic somatostatinoma is a rare entity with the diagnosis depending on pathological examination. The symptoms of the characterized "somatostatinoma syndrome" may be obscure and sometimes seemingly uncorrelated. Clinicians should review all clinical observations together to obtain an accurate diagnosis. The serum somatostatin level is elevated in most cases, whereas the imaging feature is relatively nonspecific. Most of these tumors are malignant and aggressive surgery is preferred. The adjuvant therapies for this rare disease need further investigation.

References

Anene, C., Thompson, J.S., Saigh, J., Badakhsh, S., Ecklund, R.E., 1995. Somatostatinoma: atypical presentation of a rare pancreatic tumor. *Am. J. Gastroenterol.*, **90**(5): 819-821.

Barahona-Garrido, J., Aguirre-Gutierrez, R., Gutierrez-Manjarrez, J.I., Tellez-Avila, F.I., Lopez-Arce, G., Fomperoza-Torres, A., Criales, S., Sanchez-Cortes, E., Sarti, H.M., Yamamoto-Furusho, J.K., 2009. Association of GIST and somatostatinoma in a patient with type-1 neurofibromatosis: is there a common pathway? *Am. J. Gastroenterol.*, **104**(3):797-799. [doi:10.1038/ajg.2008.133]

Cao, X.P., Liu, Y.Y., Xiao, H.P., Li, Y.B., Wang, L.T., Xiao,

P., 2009. Pancreatic somatostatinoma characterized by extreme hypoglycemia. *Chin. Med. J. (Engl.)*, **122**(14): 1709-1712.

House, M.G., Yeo, C.J., Schulick, R.D., 2002. Periampullary pancreatic somatostatinoma. *Ann. Surg. Oncol.*, **9**(9):869-874. [doi:10.1007/BF02557523]

Janson, E.T., 2005. Somatostatin analogs in the treatment of neuroendocrine gastroenteropancreatic and intrathoracic tumors. *J. Endocrinol. Invest.*, **28**(11 Suppl. International): 137-140.

Klöppel, G., Perren, A., Heitz, P.U., 2004. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann. N. Y. Acad. Sci.*, **1014**(1):13-27. [doi:10.1196/annals.1294.002]

Konomi, K., Chijiiwa, K., Katsuta, T., Yamaguchi, K., 1990. Pancreatic somatostatinoma: a case report and review of the literature. *J. Surg. Oncol.*, **43**(4):259-265. [doi:10.1002/jso.2930430414]

Larsson, L.I., Hirsch, M.A., Holst, J.J., Ingemansson, S., Kuhl, C., Jensen, S.L., Lundqvist, G., Rehfeld, J.F., Schwartz, T.W., 1977. Pancreatic somatostatinoma. Clinical features and physiological implications. *Lancet*, **309**(8013): 666-668. [doi:10.1016/S0140-6736(77)92113-4]

Levy-Bohbot, N., Merle, C., Goudet, P., Delemer, B., Calender, A., Jolly, D., Thiefin, G., Cadiot, G., 2004. Prevalence, characteristics and prognosis of MEN 1-associated glucagonomas, VIPomas, and somatostatinomas: study from the GTE (Groupe des Tumeurs Endocrines) registry. *Gastroenterol. Clin. Biol.*, **28**(11):1075-1081.

Maki, M., Kaneko, Y., Ohta, Y., Nakamura, T., Machinami, R., Kurokawa, K., 1995. Somatostatinoma of the pancreas associated with von Hippel-Lindau disease. *Intern. Med.*, **34**(7):661-665. [doi:10.2169/internalmedicine.34.661]

Marakis, G., Ballas, K., Rafailidis, S., Alatsakis, M., Patsiaoura, K., Sakadamis, A., 2005. Somatostatin-producing pancreatic endocrine carcinoma presented as relapsing cholangitis: a case report. *Pancreatology*, **5**(2-3):295-299. [doi:10.1159/000085286]

Moayedoddin, B., Booya, F., Wermers, R.A., Lloyd, R.V., Rubin, J., Thompson, G.B., Fatourechi, V., 2006. Spectrum of malignant somatostatin-producing neuroendocrine tumors. *Endocr. Pract.*, **12**(4):394-400.

Mozell, E., Stenzel, P., Woltering, E.A., Rosch, J., O'Dorisio, T.M., 1990. Functional endocrine tumors of the pancreas: clinical presentation, diagnosis, and treatment. *Curr. Probl. Surg.*, **27**(6):309-386. [doi:10.1016/0011-3840(90)90025-Z]

Nesi, G., Marcucci, T., Rubio, C.A., Brandi, M.L., Tonelli, F., 2008. Somatostatinoma: clinico-pathological features of three cases and literature reviewed. *J. Gastroenterol. Hepatol.*, **23**(4):521-526. [doi:10.1111/j.1440-1746.2007.05053.x]

Sakazaki, S., Umeyama, K., Nakagawa, H., Hashimoto, H., Kamino, K., Mitsuhashi, T., Yamaguchi, K., 1983. Pancreatic somatostatinoma. *Am. J. Surg.*, **146**(5):674-679. [doi:10.1016/0002-9610(83)90310-0]

Sato, T., Konishi, K., Kimura, H., Maeda, K., Yabushita, K., Tsuji, M., Demachi, H., Miwa, A., 2000. Strategy for pancreatic endocrine tumors. *Hepatogastroenterology*, **47**(32):537-539.

Soga, J., Yakuwa, Y., 1999. Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. *J. Exp. Clin. Cancer Res.*, **18**(1):13-22.

Stelow, E.B., Woon, C., Pambuccian, S.E., Thrall, M., Stanley, M.W., Lai, R., Mallery, S., Gulbahce, H.E., 2005. Fine-needle aspiration cytology of pancreatic somatostatinoma: the importance of immunohistochemistry for the cytologic diagnosis of pancreatic endocrine neoplasms. *Diagn. Cytopathol.*, **33**(2):100-105. [doi:10.1002/dc.20305]

Suzuki, H., Kuwano, H., Masuda, N., Hashimoto, S., Kanoh, K., Nomoto, K., Shimura, T., Katoh, H., 2008. Diagnostic usefulness of FDG-PET for malignant somatostatinoma of the pancreas. *Hepatogastroenterology*, **55**(85):1242-1245.

Tjon, A.T.R.T., Jansen, J.B., Falke, T.H., Lamers, C.B., 1994. Imaging features of somatostatinoma: MR, CT, US, and angiography. *J. Comput. Assist. Tomogr.*, **18**(3):427-431.

Tomono, H., Kitamura, H., Iwase, M., Kuze, S., Toyoda, F., Mori, N., Tamoto, E., Inuzuka, K., Fujita, H., Konishi, Y., Naito, M., Tanioka, F., 2003. A small, incidentally detected pancreatic somatostatinoma: report of a case. *Surg. Today*, **33**(1):62-65. [doi:10.1007/s005950300012]

Vinik, A.I., Strodel, W.E., Eckhauser, F.E., Moattari, A.R., Lloyd, R., 1987. Somatostatinomas, ppomas, neurotensinomas. *Semin. Oncol.*, **14**(3):263-281.

Zhang, Z.Y., Zhang, R., Wang, L., Shen, C., Yan, J.Q., Chen, Y.J., Li, Q.Y., Yang, W.P., Peng, C.H., Li, H.W., Zhou, G.W., 2008. Diagnosis and treatment of pancreatic somatostatinoma: a case report. *Chin. Med. J. (Engl.)*, **121**(22):2363-2365.