Case Report: Somatostatin Producing Teratoma, Causing Rapidly Alternating Extreme Hyperglycemia and Hypoglycemia, and Ovarian Somatostatinoma

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A 54-year-old woman presented with extremely fluctuating and symptomatic blood glucose levels. Very high levels of somatostatin and low levels of insulin, C-peptide, gastric inhibitory peptide (GIP), and glucagon-like peptide-1 (GLP-1) in peripheral blood were constantly present. A benign somatostatinoma was localized by meta-iodobenzyl guanidine iodine 123 (MIBG-I^{123}) scintigraphy and succesfully removed encapsulated in an ovarian teratoma. The patient made a complete recovery. The case described is unique with regard to clinical symptomatology and anatomic localization of the tumor.

SOMATOSTATINOMAS ARE RARE endocrine tumors. Only about 100 cases have been reported in the literature since the first descriptions.[1-3] Tumors are most often localized in the pancreas, less often in the duodenum, and seldom in the ampulla Vateri or small intestine and are usually large and highly malignant with metastases to the liver. Cardinal symptoms are diabetes, gallstones, and steatorrhoea.[4] One case with localization to the rectum[5] and 3 cases with hypoglycemia as a main feature have been published.[6,7]

The following case report describes a patient with a hitherto not described localization of a somatostatinoma and unusual instability of blood glucose levels, not easily explained by the observed values of glucoregulatory hormones.

CASE REPORT

The patient was a 54-year-old woman employeed as a bank cashier who had always been mentally and physically healthy. At the time of admission, she had for more than 1 year suffered from periodical difficulty with concentration lasting about an hour and making her incapable of attending her normal work. One month before admission, she had been diagnosed with diabetes mellitus and was taught to monitor blood glucose by GlucoTouch (Life Scan) and to put on tolbutamide and later glimepiride. Although this did not alter her condition, she realized that her periodical confusion was combined with very low blood glucose values, and the antidiabetic drug was discontinued. Several control measurements confirmed that the patient's own monitoring was in excellent accordance with glucose values obtained from the hospital laboratory. With time the hypoglycemic episodes became more frequent and invalidating, and they were separated by intervals of very high blood glucose levels accompanied by thirst and tiredness. During the last weeks before operation, the patient was treated with both prednisone and insulin to ameliorate the condition. She also complained of severe constipation with defecation about every third day.

At admission we found the patient in good mental and physical condition with no objective abnormalities. Her hemoglobin (Hgb) was 8.0 mmol/L (normal range for our laboratory, 7.5 to 9.6), erthrocyte sedimentation rate (ESR) 10 mm/h (normal range, 2 to 15 mm/h), and blood pressure (BP) 110/70 mm Hg. However, fasting blood glucose was 25 mmol/L (normal range, 3.8 to 5.0 mmol/L) and $HgbA_{1c}$ was 0.104 (normal range, 0.044 to 0.063). Home-monitoring of blood glucose through the following 14 days when she was off all medical treatment showed an intriguing spontanous fluctuation between very high and very low values (Fig 1). A 72-hour fasting test was uneventful, with blood glucose values slowly declining from 15 to 6 mmol/L and no demonstrable hyperinsulinism. Insulin antibodies were not present. Surprisingly, shortly after breaking the fast she again showed signs and symptoms of hypoglycemia (Table 1).

Table 1. 72-Hour Fasting Test

Time (H)	Glucose (mmol/L)	Insulin (pmol/L)	C-Peptide (pmol/L)	Proinsulin (pmol/L)
	(3.8-5.0)	(5-69)	(200-700)	(2.1-13.0)
0	15			
4	11			
8	11			
12	14			
16	15			
20	15	<5	170	5.0
24	7			
28	8			
32	8			
36	10			
40	7			
44	9	<5	<100	1.8
48	6			
52	6			
56	7			
60	6			
64	6			
68	5	<5	<100	1.8
72	6			
73.5	Lunch			
76	1.9			

NOTE. Normal fasting ranges in parentheses.

Signs or symptoms of pituitary or adrenal insufficiency could not be demonstated. Blood levels of prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), corticotropin (ACTH), and cortisol, as well as 24-hour excretion of epinephrine and norepinephrine, were all normal.

A high value for insulin-like growth factor-binding protein-1 (IGFBP-1) at 93 ng/mL (normal fasting range, 0.6 to 14 ng/mL) and a low free IGF-I at 0.14 ng/mL (normal fasting range for the age, 0.35 to 0.60 ng/mL) supplied by Prof Hans Ørskov, Aarhus University were in accordance with severely suppressed insulin production. IGFBP-3 was

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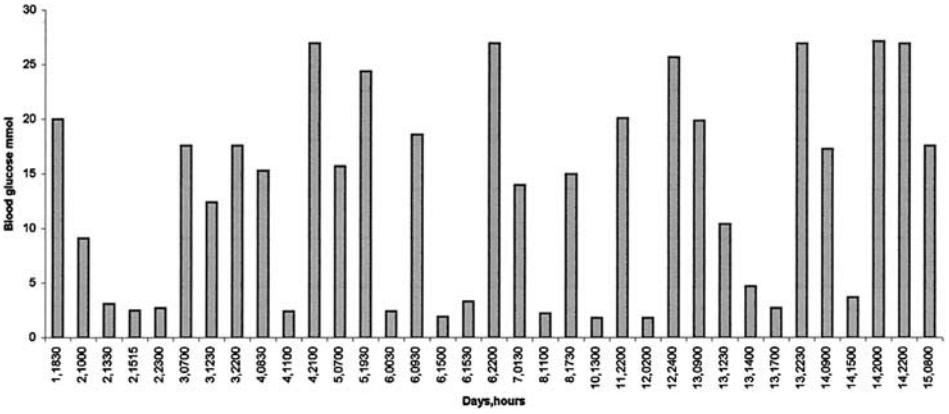

Fig 1. Home-monitoring of blood glucose during 15 consecutive days.

4,600 ng/mL (normal range for the age, 2,100 to 4,300 ng/mL). Free IGF-II was 0.87 ng/mL (normal range, 0.78 to 2.2 ng/mL). Total IGF-I was 91 ng/mL (normal range for the age group, 55 to 220 ng/mL).

Ultrasound and computed tomography scan of the abdomen initially showed no abnormalities. Gallstones were not present.

X-ray examination of the stomach showed extremely delayed emptying. Most of a test-meal was still present after 8 hours.

An oral glucose tolerance test disclosed very high levels of somatostatin with suppressed values for insulin, gastric inhibitory peptide (GIP), and glucagon-like peptide-1 (GLP-1) (Table 2). An intravenous glucose tolerance test likewise showed low insulin levels from 6 to 34 pmol/L and constantly high somatostatin levels exceeding 3,200 pmol/L.

In the search for a somatostatin-producing tumor, indium 111–octreotide scintigraphy only disclosed a vague asymmetrical accumulation in the smaller pelvis, while meta-iodobenzyl guanidine iodine 123 (MIBG-I^{123}) scintigraphy showed a very dense, round accumulation near vesica and the rectum. The accumulation was persistent after emptying the bladder.

Rectoscopy was normal but rectal ultrasound scan and magnetic resonance of the lower abdomen confirmed the presence of a mobile tumor, 6 × 9.5 cm, in the smaller pelvis. By subsequent laparotomy, the left ovary was removed and found to contain a tumor with 2 distinct parts: a softer part 7 × 4.5 cm with components of hair, sebaceous glands, smooth muscle cells, connective tissue, and epithelium typical for a teratoma, and a firmer, spherical part with a diameter of 5 cm. Microscopy of this portion demonstrated an epithelial, trabecular, encapsulated tumor with some psammoma bodies and an evenly distributed content of somatostatin by immunohistochemistry (Figs 2 through 5). Reaction to insulin, glucagon, and serotonin could not be demonstrated on repeated attemps.

The patient's general well-being and blood glucose levels stabilized as normal immediately postoperatively and have remained so for more than 1 year. Bowel function is restored as well. An oral glucose

Table 2. Pre- and Postoperative Glucose Tolerance Test

	Glucose (mmol/L)		Insulin (pmol/L)		GIP (pmol/L)		GLP-1 (pmol/L)		Somatostatin (pmol/L)	
Time (min)	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
	(3.8-5.0)		(5-69)		(0-20)		(0-25)		(0-10)	
0	16	4.1	3.5	20		7	7	10		6
15	20	4.7	<3.0	67	2	26	9	13	1,100	6
30	22	5.5	<3.0	89	4	39	8	16	1,250	5
45	25	6.2	<3.0	123	4	36	10	23	1,500	6
60	27	5.9	<3.0	111	3	53	11	19	1,750	7
90	31	7.1	<3.0	132	5	62	13	21	1,350	6
120	37		<3.0		6		17		2,300	
150	36		<3.0				21		1,500	
180	35		4.0		4		11		2,750	
240	33		3.1		4		9			
300	30		5.8				14			

NOTE. Normal fasting ranges in parentheses. GIP, GLP-1, and somatostatin concentrations in plasma were measured after extraction of plasma with 70% ethanol (vol/vol, final concentration). For the GIP radioimmunoassay,[12] we used the C-terminally directed antiserum R 65, which cross-reacts fully with human GIP but not with the socalled GIP 8000, whose chemical nature and relationship to GIP secretion is uncertain. Human GIP and ^{125}I human GIP (70 MBq/nmol) were used standards and tracer. The plasma concentrations of GLP-1 were measured[13] against standards of synthetic GLP-1 7-36amide using antiserum code no. 89390, which is specific for the amidated C-terminus of GLP-1 and therefore does not react with GLP-1–containing peptides from the pancreas. The results of the assay accurately reflect the rate of secretion of GLP-1 because the assay measures the sum of intact GLP-1 and the primary metabolite, GLP-1 9-36amide, into which GLP-1 is rapidly converted.[14] Somatostatin was measured by a previously published assay,[15] using antiserum code no. 1758, which cross-reacts equally with somatostatin 14 and somatostatin 28. For all assays, sensitivity was <1 pmol/L, intraassay coefficient of variation <6% at 20 pmol/L, and recovery of standard, added to plasma before extraction, about 100% when corrected for losses inherent in the plasma extraction procedure.

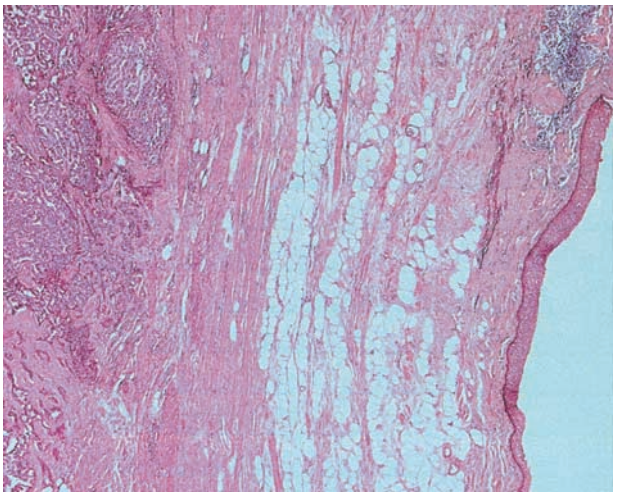

Fig 2. Ovarian stomatostatinoma: part of the somatostatinoma located deep in the wall of the cyst; tumor to the left (top), squamous epithelium lining to the right (bottom), and in between fatty and connective tissue and smoth muscle fibers. Hematoxylin and eosin staining (H&E); original magnification, 25x.

tolerance test performed 2 months after surgery showed completely normal results (Table 2).

DISCUSSION

The present case of somatostatinoma is unusual in several respects. Localization to an ovarian teratoma has not been reported previously, although teratomas with components producing other hormones such as serotonin and thyroxine have been observed.[8]

Our patient did not display gallstones or steatorrhoea but on the contrary complained of constipation. However, delayed gastric emptying as observed is a well-known effect of somatostatin, which also has been used as a therapeutic against watery diarrheas.[9]

Diabetes mellitus is a common feature in somatostatinomas but hypoglycemia has only been reported in 3 cases prior to our patient.[6,7] The former cases all looked like insulinomas with a mixed production of insulin and somatostatin. Two of the patients had only minor or no elevation of circulating plasma somatostatin, and all 3 had normal or elevated plasma insulin during hypoglycemic episodes. The patient with the highest levels of somatostatin had multiple liver metastases, which might have contributed to the patient′s hypoglycemia. Examination of the tumors showed insulin-producing as well as somatostatin-producing cells.

Our patient′s tumor did not contain insulin-producing cells and the plasma insulin levels were extremely low even during glucose stimulation. Thus, hyperinsulinemia is an unlikely ex-

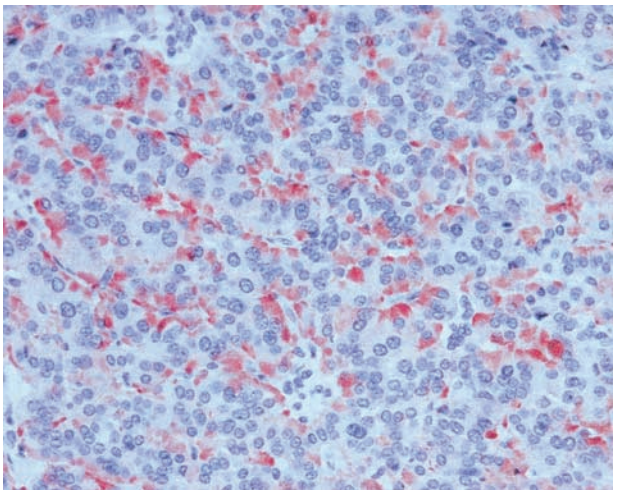

Fig 4. Ovarian somatostainoma: chromogranin A immunostaining reaction of the tumor. Original magnification, 200x.

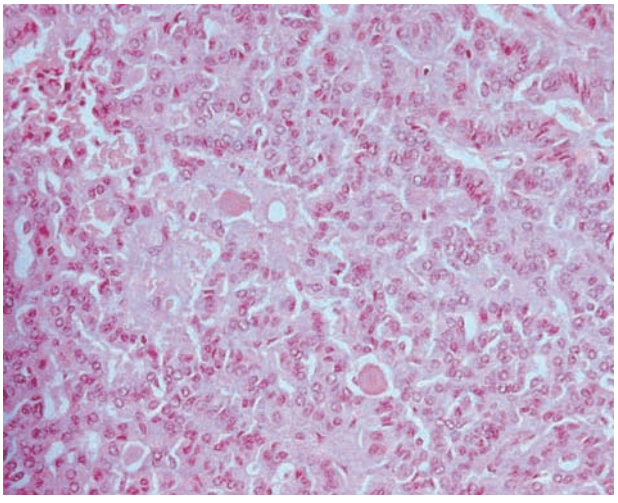

Fig 3. Ovarian somatostatinoma: close up view shows the solid, trabecular growth pattern and some (n = 2) psammoma bodies. H&E; original magnification, 200x.

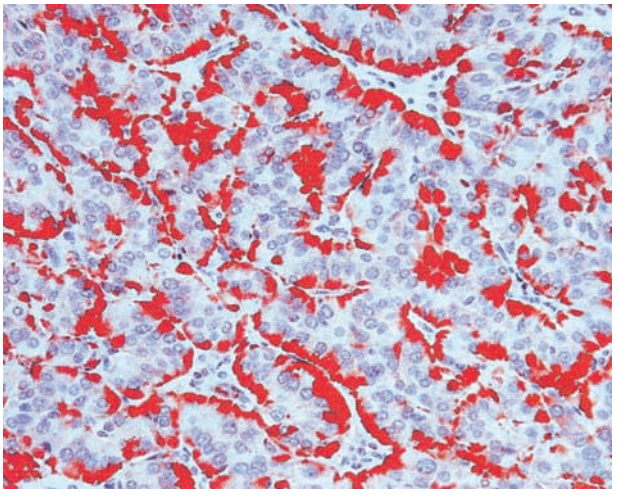

Fig 5. Ovarian somatostatinoma: somatostain immunostaining reaction of the tumor. Original magnification, 200x.

planation for the hypoglycemic attacks. The hypersomatostatinemia would be expected to also inhibit glucagon secretion. Although glucagon serves as a first-line defence against hypoglycemia, lack of glucagon does not in itself result in hypoglycemia. Thus, near complete elimination of glucagon by immunoneutralization did not result in hypoglycemia,[10] and mice with a null mutation of the glucagon receptor gene do not become hypoglycemic.[16]

The observations during oral and intravenous glucose tolerance tests indicated our patient was not unable to produce insulin, although we never observed excess amounts during basal conditions. Even so, the slow decline of blood glucose toward normal values during her 72-hour fast makes it conceivable that some insulin action had taken place, although it was not measurable in plasma. It must be considered possible that her somatostatinoma periodically suppressed glucagon to a higher extent than insulin secretion, resulting in an imbalance favoring hypoglycemia.

Our patient claimed that her hypoglycemic episodes often followed defecation or ingestion of a meal. Unfortunately, we have no systematic observations related to those statements. As reported in Table 1, we observed a hypoglycemic episode 90 minutes after breaking the 72-hour fast. According to her own home-monitoring (when not treated) most hypoglycemic episodes occurred during the first 3 hours after lunch but some episodes were experienced around midnight when she had not eaten recently. Also, the delayed emptying of the stomach makes it difficult to judge the relation between meals and the effect on blood glucose values. However, the remarkable absence of large fluctuations during her 72-hour fast is consistent with the proposal that ingestion of meals could have induced some disturbance of an internal equilibrium between gut hormones, or promoted the production of a hitherto unknown hypoglycemic hormone. In addition, the close anatomic relation between the ovarian localization and the rectum makes it conceivable that constipation and defecation could disturb this balance, possibly by physical pressure on the tumor exerted by the filled rectum.

^{111}In-octreotide has often been used with success for scintigraphic localization of carcinoid tumors. It is remarkable that in the present case MIBG-I^{123} yielded a much better result. Similar observations have been made in a few other cases of somatostatinoma.[11]

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