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The Presence of Somatostatin Receptors in Malignant Neuroendocrine Tumor Tissue Predicts Responsiveness to Octreotide

L.K. KVOLS, M.D.,[a] J.C. REUBI, M.D.,[b] U. HORISBERGER, B.S.,[b]
C.G. MOERTEL, M.D.,[a] J. RUBIN, M.D.,[a] AND J.W. CHARBONEAU, M.D.[c]

[a]*Department of Oncology and* [c]*Department of Radiology, Mayo Clinic, Rochester, Minnesota;* [b]*Sandoz Research Institute Berne, Berne, Switzerland*

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In 77 percent of patients suffering from a malignant carcinoid syndrome, administration of the somatostatin analog, octreotide (SMS 201-995, Sandostatin®) induced clinical improvement coupled with a decrease in 24-hour urinary 5-hydroxyindole acetic acid (5-HIAA). This finding prompted an evaluation to determine the correlation between the presence of somatostatin receptors in tumor tissue and the response to octreotide in patients with advanced, metastatic, neuroendocrine tumors. In tissues of 31 tumors (20 carcinoid, eight islet-cell carcinoma, three medullary thyroid carcinomas), the presence of somatostatin receptors was analyzed by binding of the somatostatin analog ^{125}I-Tyr^3-SMS 201-995 and autoradiography. Receptors were detected in 16 of 20 samples of carcinoid tissues; all but one patient with receptor-positive tumors improved clinically after treatment with octreotide, and the urine 5-HIAA level was reduced a median of 63 percent (range, 39–94 percent) compared to values before treatment. Of the receptor-negative carcinoid patients, only one showed clinical improvement, which was minimal, and there was a negligible reduction in 5-HIAA after octreotide therapy. All eight patients with metastatic islet-cell carcinomas were positive for somatostatin receptors. Symptomatic improvement and a >50 percent decrease in the level of at least one of the pathologically elevated marker hormones was seen in all eight. None of the three patients with medullary carcinoma of the thyroid had a decrease in calcitonin, and all three were initially somatostatin receptor-negative.

We conclude that the presence of somatostatin receptors in malignant neuroendocrine tumor tissue appears to correlate with the response to octreotide therapy. Analysis of somatostatin receptors in malignant neuroendocrine carcinoma tissue should be included in future prospective clinical trials of this synthetic peptide.

Malignant neuroendocrine tumors arise from different organs, which include the gastrointestinal tract, pancreas, lungs, and thyroid. The common molecular thread linking tumors from such diverse organs is the ability of the neoplastic neuroendocrine cell to incorporate amines intracellularly and to decarboxylate them. As a result, they are sometimes referred to as APUDomas (*a*mine *p*recursor *u*ptake and *d*ecarboxylation). A number of tumors from these organs secrete one or more hormones. Among these tumors are carcinoids, glucagonomas, gastrinomas, insulinomas, VIPomas, and medullary thyroid carcinomas. These tumors often grow

Abbreviations: APUD: amine precursor uptake and decarboxylation 5-HIAA: 5-hydroxyindole acetic acid SC: subcutaneous(ly)

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Address reprint requests to: L.K. Kvols, M.D., Dept. of Oncology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905

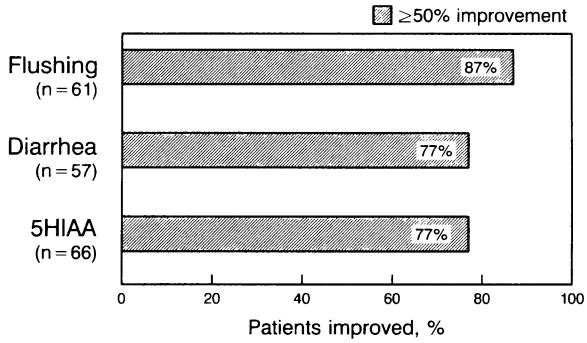

FIG. 1. Therapeutic results in the first 66 patients with the malignant carcinoid syndrome treated at the Mayo Clinic with the somatostatin analog, octreotide.

slowly, but the patient may be incapacitated or die as a result of the hormonal syndromes.

Somatostatin is a potent inhibitor of the release of pituitary and gastrointestinal hormones [1]. Therefore, this hormone and its synthetic longer-acting analogs have been considered for therapy of tumors which secrete hormones. We have treated 66 patients with metastatic carcinoid tumors and have sequentially followed them after chronic self-administration of the somatostatin analog, octreotide (SMS 201-995, Sandostatin™), using two different protocols. Thirty-one patients were started on a low-dose protocol of octreotide, 150 mcg subcutaneously (sc) three times daily. Flushing was reduced in 76 percent, and diarrhea improved in 83 percent. The median 24-hour 5-hydroxyindole acetic acid (5-HIAA) level before treatment in this group was 203 mg (normal, 0–6 mg per 24 hours). The median reduction of 5-HIAA was 69 percent with 77 percent having a major (>50 percent) reduction [2]. Thirty-five patients with no prior exposure to octreotide were started on a high-dose protocol of octreotide, 500 mcg subcutaneously three times daily. Flushing was reduced in 97 percent, and diarrhea improved in 77 percent. The median 24-hour 5-HIAA level before treatment in this group was 160 mg; in 77 percent of patients, the 5-HIAA was reduced $\geq$ 50 percent) with octreotide therapy. Considering all 66 patients then, flushing was reduced in 87 percent, diarrhea in 77 percent, and a major (≥ 50 percent) reduction in 5-HIAA was seen in 77 percent (Fig. 1).

The therapeutic results in malignant islet-cell carcinomas have been similiarly favorable, with reversal of the hormonally mediated syndromes often occurring within the first few days or weeks after initiating therapy [3]. The results delineated according to the pathologically elevated hormone are displayed in Fig. 2.

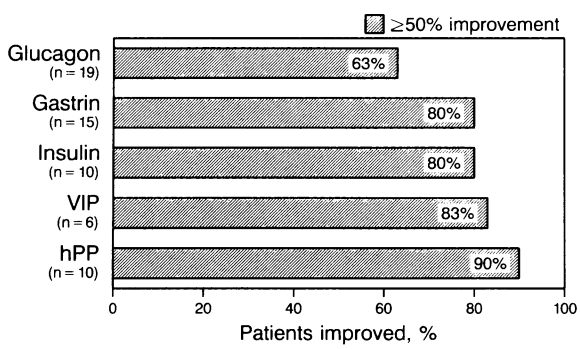

FIG. 2. Responses delineated by pathologically elevated hormones in functioning islet-cell carcinomas treated at the Mayo Clinic with the somatostatin analog, octreotide.

The precise mechanism of somatostatin's effect on these tumors has not been fully elucidated. A direct effect on tumor cells was suggested by earlier studies, which demonstrated a high incidence of somatostatin receptors in a small number of islet-cell carcinomas [4,5,6,7]. Tumor tissues from gastrinomas, VIPomas, and insulinomas were shown to contain somatostatin receptors, which suggested that perhaps they may be required for the therapeutic efficacy of somatostatin analog. To date, however, there has been no systematic evaluation correlating the tumor receptor status and *in vivo* hormonal response in malignant neuroendocrine tumors.

We have recently reported the incidence of receptors for somatostatin in a larger number of islet-cell carcinomas ($n = 15$) and carcinoid tumors ($n = 62$) [8]. Fifty-four of 62 carcinoid patients had somatostatin receptor-positive tumors (87 percent). In 15 of the islet-cell carcinomas, somatostatin receptors were detected. Of particular interest was the observation that, in biopsies of different metastases in an individual liver, similar densities of somatostatin receptors were found. This information, combined with the ability to obtain tumor tissue for analysis by percutaneous needle biopsy, suggests that this technique might be prognostically significant.

The goal of this study was to determine if the presence of somatostatin receptors in tumor cells is correlated with the hormonal responsiveness of functional neuroendocrine carcinomas to therapy with the somatostatin analog, octreotide.

METHODS

Patient Selection and Tissue Procurement

Samples of tumors from 31 patients with malignant neuroendocrine tumors were obtained by surgery ($n = 10$) or percutaneous needle biopsy ($n = 21$). The diagnosis had been established before on the basis of clinical symptoms, pathologically elevated plasma hormone levels, and histologic examination of the tumor. The study population comprised 20 patients with metastatic carcinoid tumors and the malignant carcinoid syndrome, eight patients with metastatic islet-cell carcinomas, and three patients with metastatic medullary thyroid carcinoma.

Surgical specimens were obtained from metastases or from the primary tumor if it was resected for palliative reasons. In some cases, both the primary tumor and metastases were available for receptor analysis. Percutaneous needle biopsy specimens of the liver were obtained with ultrasound guidance. A Bard® Biopty™ instrument and an 18-gauge Biopty-Cut™ biopsy needle with a sampling notch of 17 mm were used. The liver biopsy specimens, with a mean weight of 6.8 mg, were immediately deposited in a small plastic container, which was placed on dry ice. After the specimen had been flash-frozen, it was covered with tissue preservative. The plastic container was then covered, and, within 15–30 minutes, the containers were sealed in airtight plastic bags and stored at −70°C. These samples were shipped in dry ice to Berne, Switzerland. The storage time of tumors at −70°C before autoradiographic processing ranged from two to 12 weeks.

Autoradiography and Quantitation of Receptor Density

Tissue was analyzed for somatostatin receptors using autoradiography with ^{125}I-Tyr^3-SMS 201-995, a tyrosine substituted analog of octreotide (Fig. 3). The ligand was iodinated and purified according to the method of Reubi and characterized in standard binding assays [6,9]. Binding in the tested tumors was of the high-affinity type (K_D approximately one nM). The range of somatostatin receptor density

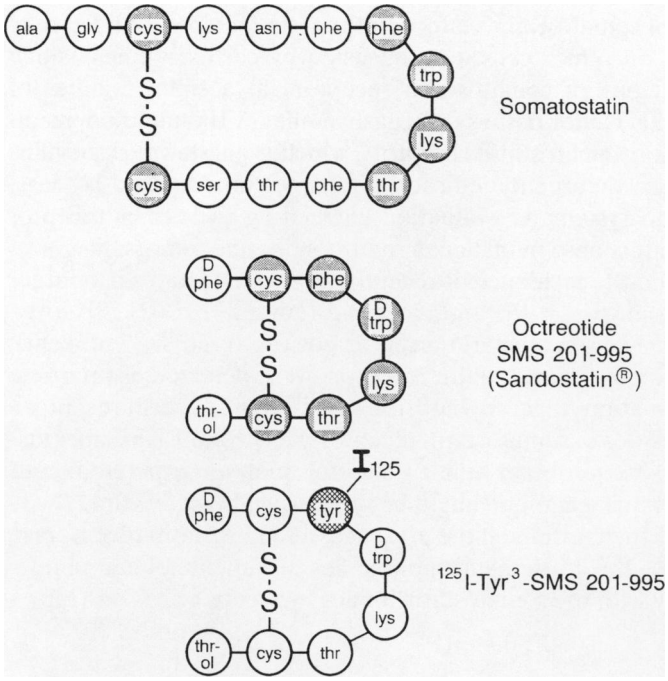

FIG. 3. Schematic depiction of the molecular structure of somatostatin 14, the synthetic somatostatin analog, octreotide, and ^{125}I-Tyr^{3}-SMS 201-995.

measured in this study lies between a few dozen fmols/mg protein to 2,000–3,000 fmols/mg protein.

Receptors' autoradiography was performed on 10 μ cryostat sections, as previously described in detail [6]. The autoradiograms were quantitatively analyzed by means of a computer-assisted image processing system, as previously described. Radioactive polymer standards for iodinated compounds (Amersham Laboratories, Little Chalfont, England) were used for this purpose [10]. Unless otherwise stated, the measured density refers to the whole tumor section.

The presence of somatostatin receptors in tumors is represented by four semiquantitative categories [6]:

$^{+++}$ represents tumors with *very strongly positive* somatostatin receptor density (> 3,000 dpm/mg tissue equivalent).

$^{++}$ represents tumors with *strongly positive* somatostatin receptor density (1,000–3,000 dpm/mg tissue equivalent).

$^{+}$ represents tumors with *positive* somatostatin receptor density (< 1,000 dpm/mg tissue equivalent).

Negative means *absence* of somatostatin receptors, defined as an optical density on the films from total binding sections lower than twice the nonspecific binding.

In Vivo *Hormonal Responses*

Hormonal responsiveness was defined as the maximum reduction in the pathologically elevated hormone after treatment with octreotide. A "major response" was ≥ 50 percent reduction, a "minor response" was 25–49 percent reduction, and "no response" was < 25 percent reduction or increase compared to the hormone level before treatment.

RESULTS

Carcinoid Patients

In the 20 patients with carcinoid tumors, the sites of origin of the tumors were as follows: small intestine, 12; bronchus, four; thymus, one; and unknown, three. The liver was the site of the biopsy in 17 patients, a lymph node in two, and a breast nodule in one. Seven of the 20 patients had been receiving octreotide chronically for periods ranging from three months up to 3.8 years. In 18 patients, as an indicator of response, we measured the 24-hour urine levels of 5-HIAA, and, in two patients, we measured levels of ACTH.

Receptors were present in 16 carcinoid patients (80 percent), and all but one of these responded clinically with a median reduction in 5-HIAA of 63 percent (range, 39–94 percent) (Table 1). In seven patients with positive (+) somatostatin receptors, the mean reduction in 5-HIAA after treatment with octreotide was 48 percent (range, 0–94). In one of these seven patients, there was no decrease in 5-HIAA, and there was only a minimal change in flushing and diarrhea. The five patients with strongly positive (++) somatostatin receptors had a mean reduction in 5-HIAA of 71 percent (range, 49–91). The four patients with very strongly positive (+++) somatostatin receptors had a mean reduction in their 5-HIAA of 67 percent (range, 56–79). One of these four patients' autoradiogram and serial hormone levels are shown in Fig. 4. There were four carcinoid patients with negative somatostatin receptors, and three had no clinical or hormonal response to therapy, while one had only slight clinical improvement and a minimal hormonal response (Fig. 5).

Islet-Cell Carcinoma Patients

All eight patients with metastatic islet-cell carcinoma had biopsy specimens which were strongly positive in three patients or very strongly positive in five patients for somatostatin receptors (Table 1, and Figs. 6, 7, and 8). None of the islet-cell carcinoma patients had been treated with octreotide prior to the biopsy. Symptomatic improvement and a ≥ 50 percent decrease in at least one of the elevated marker hormone levels was seen in all eight patients. Five of the eight patients (cases 21–25 in Table 1) were co-secreting more than one hormone. In three of these five polyfunctional tumors, all hormones elevated before therapy were reduced after therapy, but in two of the cases (21 and 24), there was a disparity in hormonal responsiveness.

Medullary Cancer of the Thyroid Patients

None of the three patients with medullary carcinoma of the thyroid had a decrease in calcitonin, and all three were initially somatostatin receptor-negative (Fig. 9). Two of the three patients were clinically unresponsive to octreotide, as reflected by stable or increasing calcitonin levels and new areas of metastases. The third patient had a mixed response, with transient partial regression of cervical lymphadenopathy.

DISCUSSION

Since 1984, we have been evaluating the synthetic peptide, octreotide, in patients with symptomatic, hormonally mediated, neuroendocrine carcinoma syndromes. In many ways, octreotide mimics the biologic actions of somatostatin, but octreotide is more resistant to degradation by peptidases in plasma because of the presence of two D-amino acids (Fig. 3). This condition results in a biological half-life of three hours

TABLE 1
Clinical and Laboratory Data in Study Patients

Case No.	Initials	Diagnosis	Biopsy	Previous Sandostatin™	Somatostatin Receptors	Maximum % Hormone Reduction	Sandostatin™ Protocol	Comment
1	BB	Small intestinal carcinoid	Liver (n)	No	+	94	LD	Major improvement in flushing and diarrhea
2	MH	Small intestinal carcinoid	Liver (n)	No	+	52	LD	Major improvement in flushing and diarrhea
3	JT	Bronchial carcinoid	Liver (n)	No	+	68	LD	Major improvement in flushing and diarrhea
4	CB	Carcinoid, primary unknown	Liver (s)	No	+	39	LD	Major improvement in flushing and diarrhea
5	OL	Small intestinal carcinoid	Liver (s)	Yes (5 months)	+	38	LD	Poor symptomatic response
6	MMc	Small intestinal carcinoid	Liver (n)	No	+	49	LD	Partial and transient symptomatic response
7	MP	Small intestinal carcinoid	Liver (n)	Yes (10 months)	+	0	LD	Minimal change in flushing or diarrhea
8	DB	Bronchial carcinoid	Liver (s)	Yes (3.8 years)	++	72	LD	Major improvement in flushing and diarrhea
9	EB	Carcinoid, primary unknown	Liver (s)	Yes (1 month)	++	52	LD	Major improvement in flushing and diarrhea
10	AG	Small intestinal carcinoid	Liver (s)	Yes (13 months)	++	90	HD	Major improvement in flushing and diarrhea
11	JK	Small intestinal carcinoid	Liver (n)	No	++	91	LD	Flushing, diarrhea, and wheezing resolved
12	MM	Small intestinal carcinoid	Liver (n)	No	++	49	LD	Major improvement in flushing and diarrhea
13	JA	Small intestinal carcinoid	Liver (n)	No	+++	63	LD	Major improvement in flushing and diarrhea
14	RH	Small intestinal carcinoid	Node	No	+++	69	LD	Major improvement in flushing and diarrhea
15	LK	Small intestinal carcinoid	Breast (s)	No	+++	79	LD	Major improvement in flushing and diarrhea

TABLE 1—*Continued*

Case No.	Initials	Diagnosis	Biopsy	Previous Sandostatin™	Somatostatin Receptors	Maximum % Hormone Reduction	Sandostatin™ Protocol	Comment
16	DE	Carcinoid, primary unknown	Liver (n)	No	+++	56	LD	Flushing, diarrhea, and wheezing resolved
17	SG	Bronchial carcinoid	Liver (n)	No	Negative	0	LD	Ectopic ACTH, prior adrenalectomy
18	AM	Thymic carcinoid	Node (s)	Yes (3 months)	Negative	0	LD	Ectopic ACTH, uncontrolled Cushing's
19	JP	Small intestinal carcinoid	Liver (n)	Yes	Negative	18	LD	Minimal change in flushing and diarrhea
20	RR	Bronchial carcinoid	Liver (n)	No	Negative	40	LD	Minimal change in flushing and diarrhea
21	JK	Metastatic ICC-polyfunctional	Node (n)	No	++		HD	Hypoglycemia resolved even though insulin progressively increased
		Glucagon				65		
		Insulin				0		
		Pancreatic polypeptide				95		
22	LM	Metastatic ICC-polyfunctional	Liver (n)	No	++		HD	Abdominal pain and diarrhea resolved
		Gastrin				80		Partial regression of liver metastases
		Glucagon				60		
		VIP				95		
		Pancreatic polypeptide				86		
23	DG	Metastatic ICC-polyfunctional	Liver (n)	No	++		HD	Dermatitis, stomatitis, and diarrhea resolved; insulin requirement decreased >50%, and then, after one year on therapy, she developed an insulinoma syndrome
		Glucagon				86		
		Gastrin				74		
		Pancreatic polypeptide				87		
		5-HIAA				93		
24	JB	Metastatic ICC-polyfunctional	Liver (s)	No	+++		HD	Progressive hepatomegaly within first month
		Gastrin				73		anaplastic histology
		Pancreatic polypeptide				46		
		VIP				17		
25	LS	Metastatic ICC-polyfunctional	Liver (n)	No	+++		HD	Rapid resolution of severe diarrhea
		VIP				95		
		Glucagon				65		
		Pancreatic polypeptide				95		

TABLE 1—*Continued*

Case No.	Initials	Diagnosis	Biopsy	Previous Sandostatin™	Somatostatin Receptors	Maximum % Hormone Reduction	Sandostatin™ Protocol	Comment
26	RS	Metastatic ICC-VIPoma	Liver (n)	No	+++	87	LD	Rapid resolution of severe diarrhea (7 liters/day)
27	JG	Metastatic ICC-VIPoma	Liver (n)	No	+++	89	LD	Resolution of fecal incontinence and diarrhea
28	JR	Metastatic ICC-glucagonoma	Liver (n)	No	+++	61	LD	Dermatitis resolved weight gain
29	TC	Medullary CA of thyroid	Liver (n)	No	Negative	0	HD	Rapid tumor progression
30	ST	Medullary CA of thyroid	Liver (n)	No	Negative	0	HD	Rapid increase in size of node after drug taper
31	RG	Medullary CA of thyroid	Liver (n)	No	Negative	13	HD	Co-secretion of ACTH which progressively increased

n, percutaneous needle biopsy
s, surgical biopsy
LD, 150 mcg, subcutaneous three times daily
HD, 500 mcg subcutaneous three times daily
Very high SS receptor density (+++) defined as >3,000 dpm/mg tissue equivalent
High SS receptor density (++) defined as 1,000–3,000 dpm/mg tissue equivalent
Low SS receptor density (+) defined as <1,000 dpm/mg tissue equivalent
Negative means absence of SS receptors defined as an optical density on the films from total binding sections lower than twice the nonspecific binding

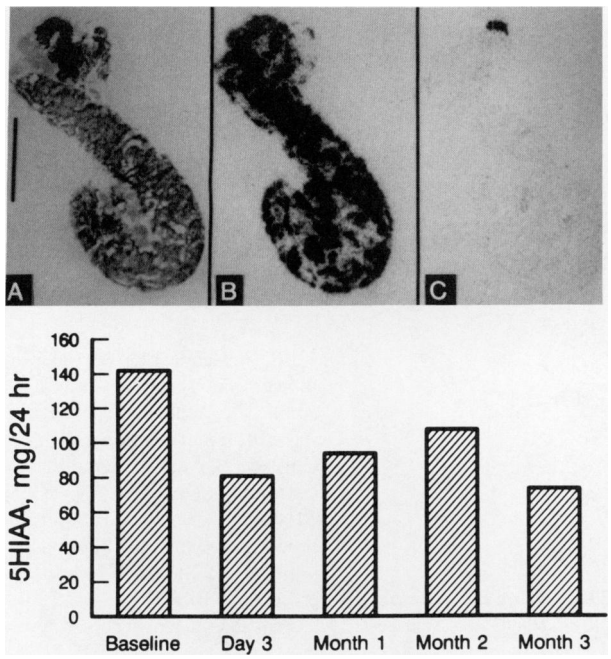

FIG. 4. Needle biopsy from liver showing metastatic carcinoid. **A.** Hematoxylin-eosin stain of tumor section (Bar = 1 mm). **B.** Autoradiogram showing total binding of ^{125}I-Tyr^3-SMS 201-995. **C.** Autoradiogram showing nonspecific binding of ^{125}I-Tyr^3-SMS 201-995 (in the presence of 10^{-6} M Tyr^3-SMS 201-995) in an adjacent section.

following subcutaneous injection, compared to the half-life of somatostatin, which is two minutes. This fact means that patients can achieve meaningful therapeutic benefit by daily administration of three subcutaneous injections.

This study establishes a strong correlation between the density of somatostatin

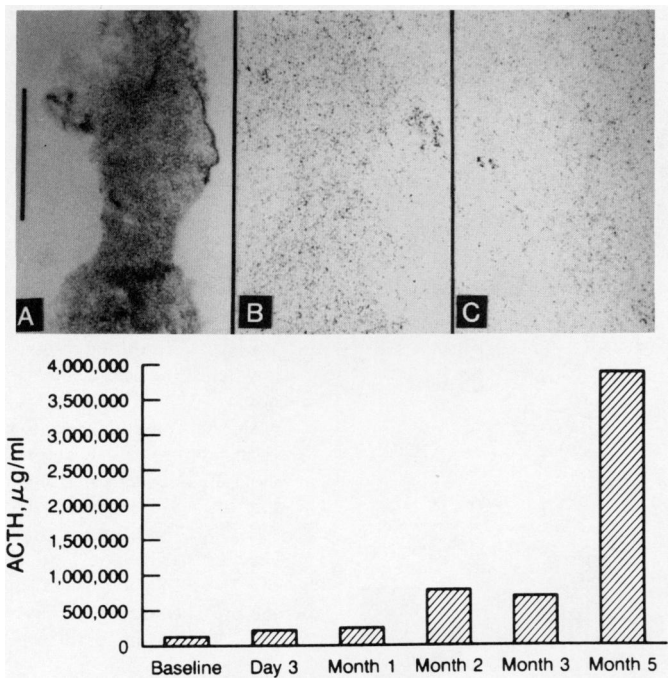

FIG. 5. Tissue biopsy showing metastatic carcinoid. **A.** Hematoxylin-eosin stain of tumor section (Bar = 1 mm). **B.** Autoradiogram showing total binding of ^{125}I-Tyr^3-SMS 201-995. **C.** Autoradiogram showing nonspecific binding of ^{125}I-Tyr^3-SMS 201-995 (in the presence of 10^{-6} M Tyr^3-SMS 201-995) in an adjacent section.

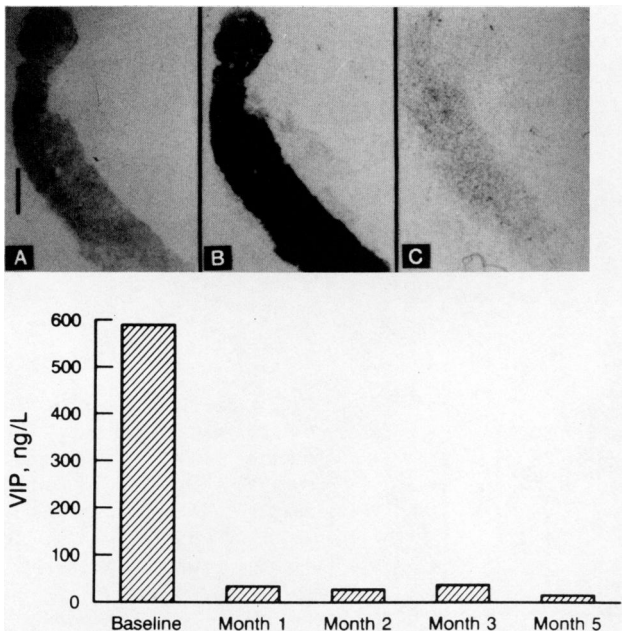

FIG. 6. Needle biopsy from liver showing metastatic islet-cell carcinoma. **A.** Hematoxylin-eosin stain of tumor section (Bar = 1 mm). **B.** Autoradiogram showing total binding of ^{125}I-Tyr^3-SMS 201-995. **C.** Autoradiogram showing nonspecific binding of ^{125}I-Tyr^3-SMS 201-995 (in the presence of 10^{-6} M Tyr^3-SMS 201-995) in an adjacent section.

receptors in neuroendocrine tumor tissue and the reduction in secretion of hormones after octreotide therapy. In 16 of the 17 patients with strongly or very strongly positive somatostatin receptors (2+ or 3+), octreotide therapy resulted in a major reduction in the concentration of circulating hormones. There was no major hormone response in any of the seven somatostatin receptor-negative patients. In the

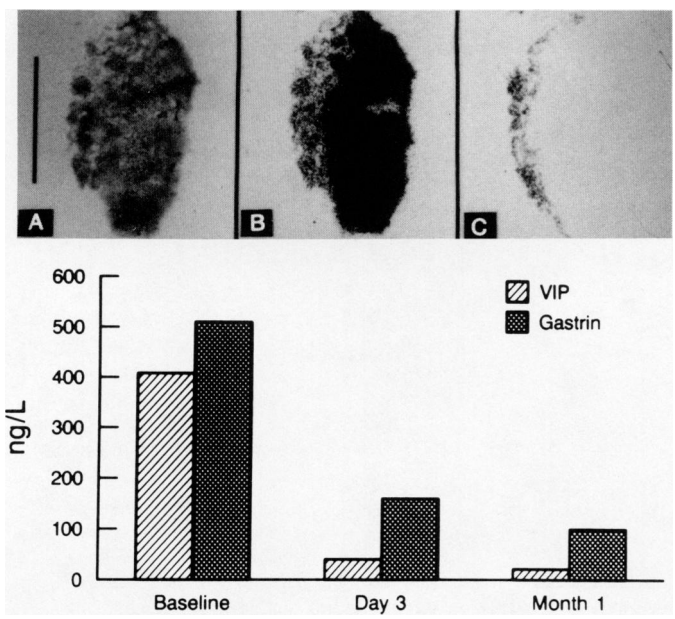

FIG. 7. Tissue biopsy showing metastatic Islet-cell carcinoma. **A.** Hematoxylin-eosin stain of tumor section (Bar = 1 mm). **B.** Autoradiogram showing total binding of ^{125}I-Tyr^3-SMS 201-995. **C.** Autoradiogram showing nonspecific binding of ^{125}I-Tyr^3-SMS 201-995 (in the presence of 10^{-6} M Tyr^3-SMS 201-995) in an adjacent section.

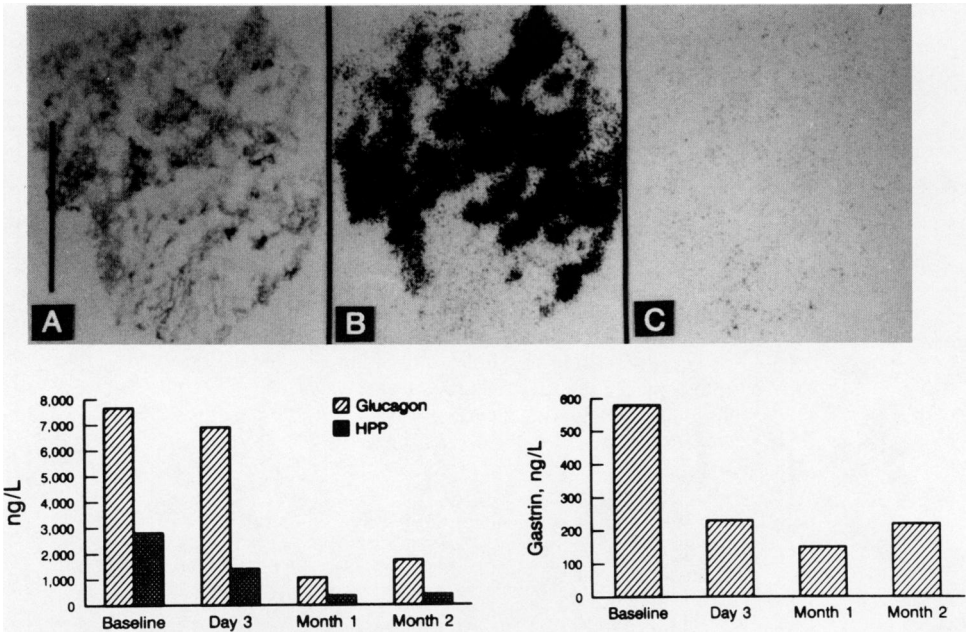

FIG. 8. Tissue biopsy showing metastatic Islet-cell carcinoma. **A.** Hematoxylin-eosin stain of tumor section (Bar = 1 mm). **B.** Autoradiogram showing total binding of ^{125}I-Tyr^3-SMS 201-995. **C.** Autoradiogram showing nonspecific binding of ^{125}I-Tyr^3-SMS 201-995 (in the presence of 10^{-6} M Tyr^3-SMS 201-995) in an adjacent section.

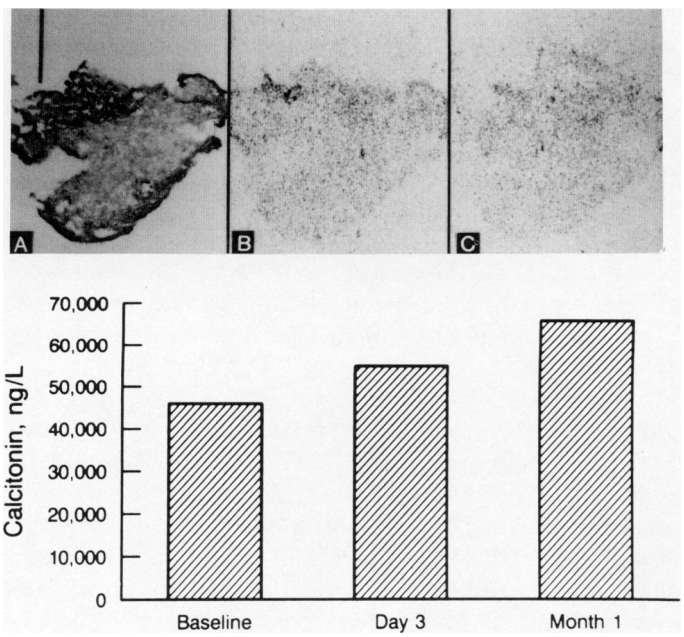

FIG. 9. Tissue biopsy showing metastatic medullary thyroid cancer. **A.** Hematoxylin-eosin stain of tumor section (Bar = 1 mm). **B.** Autoradiogram showing total binding of ^{125}I-Tyr^3-SMS 201-995. **C.** Autoradiogram showing nonspecific binding of ^{125}I-Tyr^3-SMS 201-995 (in the presence of 10^{-6} M Tyr^3-SMS 201-995) in an adjacent section.

TABLE 2
Somatostatin Receptor Status in Patients with Functional Malignant Neuroendocrine Carcinomas and the Response of Pathologically Elevated Hormones to Octreotide Therapy

	Hormonal Response		
Receptor Status	Major	Minor	No Response
+++ positive	9	0	0
++ positive	7	1	0
+ positive	3	3	1
Negative	0	1	6

+++ represents tumors with *very strongly positive* somatostatin receptor density (> 3,000 dpm/mg tissue equivalent)
++ represents tumors with *strongly positive* somatostatin receptor density (1,000–3,000 dpm/mg tissue equivalent)
+ represents tumors with *positive* somatostatin receptor density (< 1,000 dpm/mg tissue equivalent)
Negative means *absence* of somatostatin receptors (defined as an optical density on the films from total binding sections lower than twice the nonspecific binding)

seven patients with positive (1+) somatostatin receptors, one was unresponsive hormonally, and the remaining six were equally divided in the categories of major and minor hormonal responsiveness (Table 2).

Among the four somatostatin receptor-negative carcinoid patients, two had a tumor of bronchial origin, one was a thymic carcinoid, and one originated from the small intestine. Additional patients will need to be studied before we can draw any conclusions about the likelihood of somatostatin receptor status in relation to the site of origin of the carcinoid. Interestingly, the only patient with a receptor-negative metastasis from a small intestinal carcinoid later underwent palliative resection of his primary ileal tumor, and analysis of this tissue revealed strongly positive (2+) somatostatin receptors. The primary tumor was well differentiated, whereas the metastatic disease in the liver was anaplastic. It is certainly conceivable that anaplastic tissue might have lost expression of somatostatin receptors. This correlation between more dedifferentiated histology and absence of somatostatin receptors has been observed previously in breast carcinomas, central nervous system tumors, and exocrine pancreatic tumors [11–14].

Seven patients had received octreotide therapy prior to having tumor biopsies analyzed for somatostatin receptors. Two were somatostatin-negative; one was the patient discussed above with dedifferentiated liver metastases, and the other was the patient with a thymic carcinoid associated with ectopic ACTH production.

The levels of ACTH and cortisol in this patient were not affected by octreotide at doses ranging from 450–1,500 mcg/day. During a bilateral adrenalectomy for control of her Cushing's syndrome, a metastatic retroperitoneal lymph node was removed for analysis of somatostatin receptors. The other patient with a tumor co-secreting ACTH suffered from a bronchial carcinoid and was also negative for somatostatin receptors. She also underwent bilateral adrenalectomy to control her Cushing's syndrome and had normal levels of cortisol at the time of liver biopsy for somatostatin receptors. The hypercortisol state at the time the biopsy was taken in the one

patient is noteworthy because of previous observations that corticosteroids cause downregulation of somatostatin receptors [15,16]. We have never seen suppression of ectopic ACTH after octreotide therapy in six other patients with carcinoid tumors that were producing ACTH whether or not they had normal cortisols [unpublished series without somatostatin receptor data]. Additional patients will need to be studied in order to answer this important question.

In patients with polyfunctional islet-cell carcinomas (pathologically elevated plasma levels of two or more hormones), levels of one or more hormones may be unaffected by octreotide while others are markedly decreased. Patient No. 24 (JB) had a major reduction in gastrin concentration without any significant decrease in VIP levels. In other patients, one hormone could escape from initial suppression by octreotide while the other hormones remained suppressed. Patient No. 21 (JK) was somatostatin receptor-positive and experienced no decrease in insulin level, but he became euglycemic and has had stability of his tumor for the past year on octreotide. Patient No. 23 had been on therapy with octreotide for one year with continued suppression of gastrin, glucagon, pancreatic polypeptide, and 5-HIAA when she developed hyperinsulinemia and hypoglycemia.

The patient with medullary thyroid cancer who exhibited a mixed response is particularly interesting. This 62-year-old male had biopsy-proven lymph nodal metastases and osteoblastic skeletal metastases. Prior to therapy with octreotide, a liver biopsy positive for malignancy was found negative for somatostatin receptors. After eight months of therapy with octreotide at a dose of 500 mcg three times daily, the cervical lymphadenopathy had partially regressed, while the bone scan, liver metastases, and calcitonin levels remained stable. Symptomatic steatorrhea prompted a dosage reduction of octreotide, which was reduced to 250 mcg three times daily and then 150 three times daily over a period of one week. Toward the end of the week of dosage reduction, the cervical adenopathy rapidly enlarged to more than twice its original size, causing severe local pain. The node was removed for palliation, and this tissue revealed no nodal hemorrhage or necrosis as a cause for the rapid enlargement. This malignant tissue was positive for somatostatin receptors.

This study did not address alternate mechanisms by which octreotide may exert its hormonal and antiproliferative effects. Growth inhibition with octreotide has been demonstrated by Reubi in two transplantable tumors. One is a rat chondrosarcoma, which contains no somatostatin receptors, and the other is a rat insulinoma, which does contain somatostatin receptors. Whether the anti-neoplastic action of octreotide is a direct effect, or an indirect effect through inhibition of growth hormone, insulin, or other tumor growth factors is unknown.

In conclusion, analysis of somatostatin receptors can be performed on small specimens of tumor tissue obtained by percutaneous needle biopsy if the specimen can be immediately frozen at −70°C. Twenty-four of 31 (77 percent) of patients with functional neuroendocrine carcinomas had positive somatostatin receptor assays. The somatostatin receptor status appears to correlate with response to therapy with the somatostatin analog, octreotide. Somatostatin receptor analysis could be included in future prospective studies of these uncommon neuroendocrine tumors to confirm the correlation of hormonal responses with the presence of receptors and to determine if the interval to progression while on therapy and the overall survival are related to receptor status.

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