A Primary Pancreatic Carcinoid Tumor with Unusual Clinical Complaints – A Case Report

a report by
Olivier Saint-Marc,[1,2] **Andrea Cogliandolo**,[2]
Alessandro Pozzo[2] *and* **Rocco Roberto Pidoto**[2]

DOI: 10.17925/OHR.2005.00.00.34

1. Editorial Board, *World Journal of Surgical Oncology*

2. Service de Chirurgie Digestive et Endocrinienne, Hospital de La Source

Introduction

Although carcinoid tumors are the most frequently occurring neuroendocrine tumors, their pancreatic localization is exceedingly rare, and often accidental.[1] In the largest published series of 8,305 cases of carcinoid tumors by Modlin and Sandor,[2] only 46 (0.55%) were in the pancreas. Unless metastatic or compressing the pancreatic duct, carcinoid tumors of the pancreas are asymptomatic, with normal levels of serotonin and its metabolites in plasma and urine.[3] Although the exact ratio of functioning versus non-functioning carcinoid tumors is not yet known, for pancreatic tumors it was estimated to be 1:10.[4] In contrast, there are pancreatic carcinomas with neuroendocrine characteristics and carcinoid-like symptoms.[5] For these reasons, a late diagnosis and a consequent poor prognosis are usual patterns for pancreatic carcinomas. In the Modlin and Sandor series, at the time of diagnosis, 76% of pancreatic carcinoid tumors were non-localized, and the five-year survival rate was only 34.1%.

In the recent revised classification of neuroendocrine tumors,[6] the size of 2cm seems to be a crucial value over which carcinoid tumors start to exhibit malignant behavior. In other words, if resection is accomplished in time, no local recurrence might be encountered and a normal survival might be expected in the absence of metastatic disease.[7] This article reports on a case of a primary pancreatic carcinoid tumor with unusual clinical presentation that induced the authors to describe some insights on these infrequent tumors.

Case Report

A 62-year-old woman was referred to the Hospital de La Source in February 1999 for intermittent epigastric pain and nausea, not always in relation to a meal. Clinical complaints of the patient began 12 months before observation. During this period, her blood tests, upper gastrointestinal (GI) endoscopy and abdominal computerized tomographic (CT) scan were found to be normal. Abdominal ultrasonography detected a 15mm hypoechoic lesion in the pancreas, and dilatation of proximal pancreatic duct. In the past, the patient had undergone appendectomy, subtotal hysterectomy, a surgical treatment of the left shoulder for traumatic lesion of ligaments, and surgical removal of a left benign breast nodule. During the previous year, the patient had suffered due to left leg phebitis complicated by minimal pulmonary embolism. She had a history of moderate smoking and alcohol intake for a long period of time and had been taking medicines (tranquillisers, vasodilators, antacids, analgesics). There was no history of weight loss. An abdominal examination did not evidence any abnormality.

Her hematological and biochemical parameters were unremarkable. Serum amylase and lipase levels were within normal range. Serum carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 levels were not elevated. Serum gastrin, glucagon, insulin, and vasoactive intestinal polypeptide (VIP) levels were within normal limits. Urinary 5-hydroxyindoleacetic acid (5-HIAA) levels were normal, but serum serotonin level was elevated on three occasions (430, 365 and 370U/l respectively).

1. *Buchanan K D, Johnston C F, O'Hare M M, Ardill J E, Shaw C, Collins J S, Watson R G, Atkinson A B, Hadden D R, Kennedy T L, et al., "Neuroendocrine tumours. A European view",* Am. J. Med. *(1986), 81 (Suppl 6B): pp. 14–22.*
2. *Modlin I M and Sandor A, "An analysis of 8305 cases of carcinoid tumours",* Cancer *(1997), 15: pp. 813–829.*
3. *Feldman J M, "Carcinoid tumour and the carcinoid syndrome",* Curr. Probl. Surg. *(1989), 26: pp. 835–885.*
4. *Creutzfeldt W, "Endocrine tumours of the pancreas", In: Volk B W, Arquilla E R (eds) "The diabetic pancreas", New York, Plenum Publishing Corporation (1985), pp. 543–586.*
5. *Eusebi V, Capella C, Bondi A, Sessa F, Vezzadini P and Mancini A M, "Endocrine pancreatic cells in pancreatic exocrine carcinomas",* Histopathology *(1981), 5: 599–613.*
6. *Capella C, Heitz P U, Hoefler H, Solcia E and Kloeppel G., "Revised classification of neuroendocrine tumours of the lung, pancreas and gut",* Virchows. Arch. *(1995), 425: pp. 547–560.*
7. *Maurer C A, Baer H U, Dyong T H, Mueller-Garamvoelgyi E, Friess H, Ruchti C, Reubi J C and Buchler M W, "Carcinoid of the pancreas: clinical characteristics and morphological features",* Eur. J. Cancer *(1996), 7: pp. 1,109–1,116.*

AT THE FIRST SIGN OF CARCINOID SYNDROME…

Change Their World

Sandostatin LAR® Depot Works at the Site of Carcinoid Tumors to Reduce 5-HIAA Levels and Control Diarrhea and Flushing*[1,2]

Once-A-Month

Sandostatin LAR® Depot

(octreotide acetate for injectable suspension)

The Power of Control. Made Easy.

1-877-LAR-HELP **www.us.sandostatin.com**

Please see Brief Summary of Prescribing Information on adjacent page.

*Patients with carcinoid tumors often experience symptom flare-ups while being maintained on SC Sandostatin® Injection or Sandostatin LAR® Depot. They may be given SC Sandostatin® Injection for a few days (at the dosage they were receiving prior to switch to Sandostatin LAR® Depot) until symptoms are again controlled.

References: **1.** Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol.* 1999; 17:600-606. **2.** Sandostatin LAR® Depot (octreotide acetate for injectable suspension) Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2004.

NOVARTIS ONCOLOGY

Sandostatin LAR® Depot

(octreotide acetate for injectable suspension)

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE: Acromegaly: Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is indicated for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate Sandostatin® (octreotide acetate) Injection. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Sandostatin LAR® Depot can be used in patients who have had an inadequate response to surgery or in those for whom surgical resection is not an option. It may also be used in patients who have received radiation and have had an inadequate therapeutic response *(see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION in the full prescribing information).*

Carcinoid Tumors: Sandostatin LAR® Depot is indicated for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors in patients in whom initial treatment with Sandostatin® Injection has been shown to be effective and tolerated.

Vasoactive Intestinal Peptide Tumors (VIPomas): Sandostatin LAR® Depot is indicated for long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors in patients in whom initial treatment with Sandostatin® Injection has been shown to be effective and tolerated.

In patients with acromegaly, carcinoid syndrome and VIPomas, the effect of Sandostatin® Injection and Sandostatin LAR® Depot on tumor size, rate of growth and development of metastases, has not been determined.

CONTRAINDICATIONS: Sensitivity to this drug or any of its components.

WARNINGS: Adverse events that have been reported in patients receiving Sandostatin® (octreotide acetate) Injection can also be expected in patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). Incidence figures in the *WARNINGS* and *ADVERSE REACTIONS* sections, below, are those obtained in clinical trials of Sandostatin® Injection and Sandostatin LAR® Depot.

Gallbladder and Related Events: Single doses of Sandostatin® Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin® Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin® Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR® Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

In clinical trials 62% of malignant carcinoid patients who received Sandostatin LAR® Depot for up to 18 months developed new biliary abnormalities including gallstones, sludge and dilatation. New gallstones occurred in a total of 24% of patients.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin® Injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

PRECAUTIONS *(See ADVERSE REACTIONS.):* General: Growth hormone secreting tumors may sometimes expand and cause serious complications (e.g., visual field defects). Therefore, all patients with these tumors should be carefully monitored.

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Octreotide also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with octreotide.

Glucose Metabolism: The hypoglycemia or hyperglycemia which occurs during octreotide therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin® (octreotide acetate) Injection therapy was reported in one patient with no history of hyperglycemia *(see ADVERSE REACTIONS).*

In patients with concomitant Type **I** diabetes mellitus, Sandostatin Injection and Sandostatin LAR® Depot (octreotide acetate for injectable suspension) are likely to affect glucose regulation, and insulin requirements may be reduced. Symptomatic hypoglycemia, which may be severe, has been reported in these patients. In non-diabetics and Type **II** diabetics with partially intact insulin reserves, Sandostatin Injection or Sandostatin LAR Depot administration may result in decreases in plasma insulin levels and hyperglycemia. It is therefore recommended that glucose tolerance and antidiabetic treatment be periodically monitored during therapy with these drugs.

Thyroid Function: Hypothyroidism has been reported in acromegaly and carcinoid patients receiving octreotide therapy. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic octreotide therapy *(see ADVERSE REACTIONS).*

Cardiac Function: In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease *(see PRECAUTIONS).* Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin® Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge *(see ADVERSE REACTIONS).*

Nutrition: Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B_{12} levels is recommended during therapy with Sandostatin LAR® Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

Information for Patients: Patients with carcinoid tumors and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms.

Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

Laboratory Tests: Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

> Responsiveness to octreotide may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours after subcutaneous injection of Sandostatin® Injection (not Sandostatin LAR® Depot). Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of Sandostatin® Injection or dosage change. After patients are switched from Sandostatin® Injection to Sandostatin LAR® Depot, GH and IGF-1 determinations may be made after 3 monthly injections of Sandostatin LAR® Depot. (Steady-state serum levels of octreotide are reached only after a period of 3 months of monthly injections.) Growth hormone can be determined using the mean of 4 assays taken at 1-hour intervals. Somatomedin C can be determined with a single assay. All GH and IGF-1 determinations should be made 4 weeks after the previous Sandostatin LAR® Depot.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide)

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy *(see PRECAUTIONS - General).*

Drug Interactions: Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

Drug Laboratory Test Interactions: No known interference exists with clinical laboratory tests, including amine or peptide determinations.

Carcinogenesis/Mutagenesis/Impairment of Fertility: Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin®. No mutagenic potential of the polymeric carrier in Sandostatin LAR® Depot, D,L-lactic and glycolic acids copolymer, was observed in the Ames mutagenicity test.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85-99 weeks at doses up to 2000 mcg/kg/day (8x the human exposure based on body surface area). In a 116-week subcutaneous study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10x the human exposure based on body surface area) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin® Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7x the human exposure based on body surface area.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to octreotide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin LAR® Depot is administered to a nursing woman.

Pediatric Use: Sandostatin LAR® Depot has not been studied in pediatric patients.

Experience with Sandostatin® Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal-steatorrhea, diarrhea, vomiting and abdominal distention. Poor growth has been reported in several patients treated with Sandostatin® Injection for more than 1 year; catch-up growth occurred after Sandostatin® Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin® Injection.

ADVERSE REACTIONS *(See WARNINGS and PRECAUTIONS.):* Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic octreotide therapy *(see WARNINGS).* Few patients, however, develop acute symptoms requiring cholecystectomy.

Cardiac: In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin® (octreotide acetate) Injection therapy. Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). In carcinoid syndrome patients sinus bradycardia developed in 19%; conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease *(see PRECAUTIONS).*

Gastrointestinal: The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 4.

Table 4
Number (%) of Acromegalic Patients with Common G.I. Adverse Events

	Sandostatin® Injection S.C. t.i.d. n=114		Sandostatin LAR® Depot q. 28 days n=261	
Adverse Event	**N**	**%**	**N**	**%**
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Nausea	34	(29.8)	27	(10.3)
Vomiting	5	(4.4)	17	(6.5)

Only 2.6% of the patients on Sandostatin® Injection in U.S. clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR® Depot discontinued therapy for a G.I. event.

In patients receiving Sandostatin LAR® Depot the incidence of diarrhea was dose related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR® Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR® Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Hypo/Hyperglycemia: In acromegaly patients treated with either Sandostatin® Injection or Sandostatin LAR® Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients. In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR® Depot *(see PRECAUTIONS).*

Hypothyroidism: In acromegaly patients receiving Sandostatin® Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin® Injection. In acromegalics treated with Sandostatin LAR® Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR® Depot, required initiation of thyroid hormone replacement therapy. In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported *(see PRECAUTIONS).*

Pain at the Injection Site: Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg and 30 mg, respectively, of Sandostatin LAR® Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

Other Adverse Events 16%-20%: Other adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR® Depot were upper respiratory infection, flu-like symptoms, fatigue, dizziness, headache, malaise, fever, dyspnea, back pain, chest pain, arthropathy.

Other Adverse Events 5%-15%: Other adverse events (relationship to drug not established) occurring in an incidence of 5%-15% in patients receiving Sandostatin LAR® Depot were: ***Body As a Whole:*** asthenia, rigors, allergy; ***Cardiovascular:*** hypertension, peripheral edema; ***Central and Peripheral Nervous System:*** paresthesia, hypoesthesia; ***Gastrointestinal:*** dyspepsia, anorexia, hemorrhoids; ***Hearing and Vestibular:*** earache; ***Heart Rate and Rhythm:*** palpitations; ***Hematologic:*** anemia; ***Metabolic and Nutritional:*** dehydration, weight decrease; ***Musculoskeletal System:*** myalgia, leg cramps, arthralgia; ***Psychiatric:*** depression, anxiety, confusion, insomnia; ***Resistance Mechanism:*** viral infection, otitis media; ***Respiratory System:*** coughing, pharyngitis, rhinitis, sinusitis; ***Skin and Appendages:*** rash, pruritus, increased sweating; ***Urinary System:*** urinary tract infection, renal calculus

Other Adverse Events 1%-4%: Other events (relationship to drug not established), each occurring in an incidence of 1%-4% in patients receiving Sandostatin LAR® Depot and reported by at least 2 patients were: ***Application Site:*** injection site inflammation; ***Body As a Whole:*** syncope, ascites, hot flushes; ***Cardiovascular:*** cardiac failure, angina pectoris, hypertension aggravated; ***Central and Peripheral Nervous System:*** vertigo, abnormal gait, neuropathy, neuralgia, tremor, dysphonia, hyperkinesia, hypertonia; ***Gastrointestinal:*** rectal bleeding, melena, gastritis, gastroenteritis, colitis, gingivitis, taste perversion, stomatitis, glossitis, dry mouth, dysphagia, steatorrhea, diverticulitis; ***Hearing and Vestibular:*** tinnitus; ***Heart Rate and Rhythm:*** tachycardia; ***Liver and Biliary:*** jaundice; ***Metabolic and Nutritional:*** hypokalemia, cachexia, gout, hypoproteinemia; ***Platelet, Bleeding, Clotting:*** pulmonary embolism, epistaxis; ***Psychiatric:*** amnesia, somnolence, nervousness, hallucinations; ***Reproductive, Female:*** menstrual irregularities, breast pain; ***Reproductive, Male:*** impotence; ***Resistance Mechanism:*** cellulitis, renal abcess, moniliasis, bacterial infection; ***Respiratory System:*** bronchitis, pneumonia, pleural effusion; ***Skin and Appendages:*** alopecia, urticaria, acne; ***Urinary System:*** incontinence, albuminuria; ***Vascular:*** cerebral vascular disorder, phlebitis, hematoma; ***Vision:*** abnormal vision

Rare Adverse Events: Other events (relationship to drug not established) of potential clinical significance occurring rarely (<1%) in clinical trials of octreotide either as Sandostatin® Injection or Sandostatin LAR® Depot, or reported post-marketing in patients with acromegaly, carcinoid syndrome, or other disorders include: ***Body As a Whole:*** anaphylactoid reactions, including anaphylactic shock, facial edema, generalized edema, abdomen enlarged, malignant hyperpyrexia; ***Cardiovascular:*** aneurysm, myocardial infarction, angina pectoris, aggravated, pulmonary hypertension, cardiac arrest, orthostatic hypotension; ***Central and Peripheral Nervous System:*** hemiparesis, paresis, convulsions, paranoia, pituitary apoplexy, visual field defect, migraine, aphasia, scotoma, Bell's palsy; ***Endocrine Disorders:*** hypoadrenalism, diabetes insipidus, gynecomastia, galactorrhea; ***Gastrointestinal:*** G.I. hemorrhage, intestinal obstruction, hepatitis, increase in liver enzymes, fatty liver, peptic/gastric ulcer, gallbladder polyp, appendicitis, pancreatitis; ***Hearing and Vestibular:*** deafness; ***Heart Rate and Rhythm:*** atrial fibrillation; ***Hematologic:*** pancytopenia, thrombocytopenia; ***Metabolic and Nutritional:*** renal insufficiency, creatinine increased, CK increased, diabetes mellitus; ***Musculoskeletal:*** Raynaud's syndrome, arthritis, joint effusion; ***Neoplasms:*** breast carcinoma, basal cell carcinoma; ***Platelet, Bleeding, and Clotting:*** arterial thrombosis of the arm; ***Psychiatric:*** suicide attempt, libido decrease; ***Reproductive, Female:*** lactation, nonpuerperal; ***Respiratory:*** pulmonary nodule, status asthmaticus, pneumothorax; ***Skin and Appendages:*** cellulitis, petechiae, urticaria; ***Urinary System:*** renal failure, hematuria; ***Vascular:*** intracranial hemorrhage, retinal vein thrombosis; ***Vision:*** glaucoma

Antibodies to Octreotide: Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin® Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR® Depot.

Storage: For prolonged storage, Sandostatin LAR® Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. Sandostatin LAR® Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

REV: APRIL 2004

T2004-23
89018502

Sandostatin LAR® Depot vials are manufactured by:
Biochemie GmbH, Schaftenau, Austria
(Subsidiary of Novartis Pharma AG, Basle, Switzerland)

The diluent syringes are manufactured by:
Solvay Pharmaceuticals B.V.
Olst, The Netherlands

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

AT THE FIRST SIGN OF CARCINOID SYNDROME…

Change Their World

Sandostatin LAR® Depot Works at the Site of Carcinoid Tumors to Reduce 5-HIAA Levels and Control Diarrhea and Flushing*[1,2]

Once-A-Month
Sandostatin LAR® Depot
(octreotide acetate for injectable suspension)

1-877-LAR-HELP **www.us.sandostatin.com**

The Power of Control. Made Easy.

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is indicated for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors and for the long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors in patients in whom initial treatment with subcutaneous (SC) Sandostatin® (octreotide acetate) Injection has been shown to be effective and tolerated.

As with SC Sandostatin® Injection, the most frequently reported drug-related adverse events were biliary disorders (62%), gastrointestinal disorders (14% to 38%), and injection-site pain (20% to 50%). Hypoglycemia (4%), hyperglycemia (27%), sinus bradycardia (19%), conduction abnormalities (9%), and arrhythmias (3%) have been reported. *Contraindications:* sensitivity to this drug or any of its components.

Please see Brief Summary of Prescribing Information on adjacent page.

*Patients with carcinoid tumors often experience symptom flare-ups while being maintained on SC Sandostatin® Injection or Sandostatin LAR® Depot. They may be given SC Sandostatin® Injection for a few days (at the dosage they were receiving prior to switch to Sandostatin LAR® Depot) until symptoms are again controlled.

References: 1. Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol.* 1999; 17:600-606. **2.** Sandostatin LAR® Depot (octreotide acetate for injectable suspension) Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2004.

NOVARTIS ONCOLOGY

Figure 1: Pre-operative Localization of the Tumor with Endoscopic Ultrasonograhy

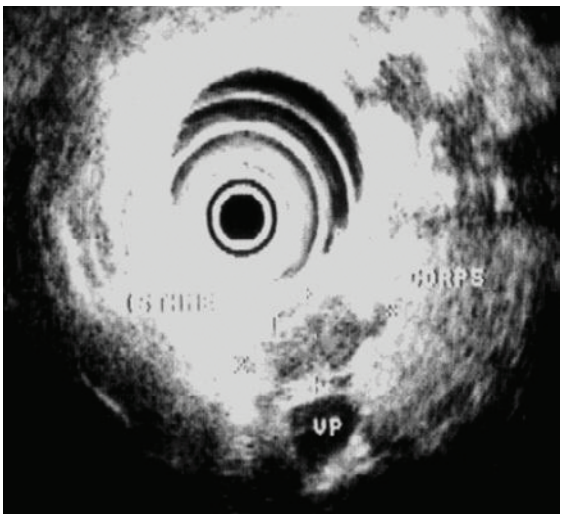
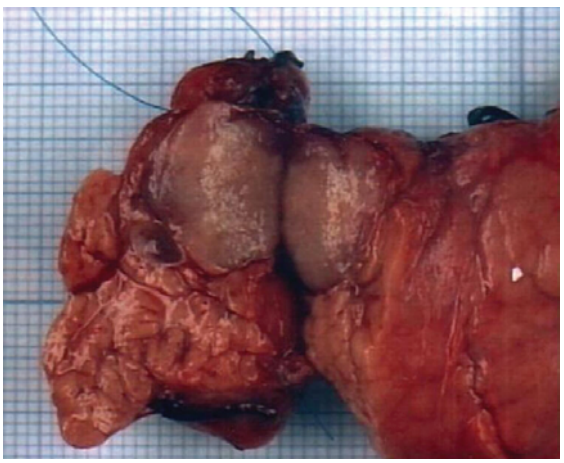


Figure 2: Gross Appearance of the Tumor in a Cross-section of the Pancreatic Specimen



Repeat CT scan of the upper abdomen and an endoscopic retrograde cholangiopancreatography failed to reveal any pathology.

An endoscopic ultrasonography was performed with a mechanical sector scanner (Olympus® GF-UM 20, Hamburg, Germany), which detected a 20x10mm hypoechogenic tumor located at the junction of the isthmus and body of the pancreas, confirming a previous ultrasonographic report (see *Figure 1*). However, there was no sign of proximal pancreatic duct dilatation or of vascular invasion or metastatic disease, as reported on earlier ultrasonographic examination. Somatostatin receptor scintigraphy with ^{111}Indium labeled pentreotide (Octroscan®, Mallinckrodt, Petten, The Netherlands) revealed an accumulation of the radioligand in the region of the suspected tumor, and confirmed the absence of metastatic disease.

In view of a localized pancreatic neoplasm, a surgical removal of the tumor was planned. At laparotomy, a pancreatic tumor was found by palpation on the left side of the portal vein. This was confirmed by intra-operative ultrasonography, which showed a hypo-echogenic, well-defined tumor, located between isthmus and corpus of the pancreas. The rest of the pancreas appeared normal. There was no evidence of metastasis in the liver and rest of the peritoneal cavity. Left spleno-pancreatectomy (distal pancreatectomy and splenectomy) with splenic, celiac, and hepatic lym-phadenectomy was accomplished.

Gross examination (see *Figure 2*) of the cut specimen showed a tumor that was not dilated near but not compressing the pancreatic duct. There was no evident involvement of celiac, hepatic, or splenic lymph nodes. On microscopic examination the cell arrangement appeared compatible with a neuroendocrine tumor. The argentaffin reaction of Fontana–Masson was negative while the argyrophil reaction of Grimelius was positive. Immunohistochemistry demonstrated 100% tumor cell staining with chromogranine, anti-neuron-specific enolase (NSE), and anti-synaptophysine antibodies. Staining with antibodies for gastrin, VIP, glucagon, and insulin were negative. Tumor cells displayed strong immuno-reactivity to anti-serotonin antibodies.

The above findings on pathological examination were conclusive of a diagnosis of a benign or low-grade malignant (functioning, well differentiated, non-angioinvasive) neuroendocrine embryonal carcinoma (EC) cell (carcinoid) tumor of the pancreas in the Capella classification.[6]

One year after her operation, the patient was free of symptoms, her serum levels of serotonin were within normal limits, and she had no signs of distant metastases.

Discussion

Carcinoid tumors can no longer be considered a rare disease, with reports being published in medical literature on large numbers of patients.[2,8] Their incidence varies from 2.1 per 100,000 population per year[2] to 8.4 per 100,000 population per year.[9] It is likely that a significant percentage of carcinoid tumors remain asymptomatic and undetected during the lifetime of an individual.

According to their embryological origin, these tumors are

8. *Godwin J D, "Carcinoid tumours. an analysis of 2837 cases",* Cancer *(1975), 36: pp. 560–569.*
9. *Berge T and Linell F, "Carcinoid tumours. Frequency in a defined population during a 12-year-period",* Acta. Pathol. Microbiol. Scand. *(1976), 844: pp. 322–330.*

classified into fore-gut carcinoid (respiratory tract, pancreas, stomach, proximal duodenum), mid-gut carcinoid (jejunum, ileum, appendix, Meckel's diverticulum, ascending colon), and hind-gut (transverse and descending colon, rectum) carcinoid tumors.[10] This distinction may be useful, as carcinoid tumors from different areas have different clinical manifestations, humoral products, and immuno-histochemical features. Most of the classic syndromes relating to the overproduction of gastrointestinal and pancreatic hormones originate from fore-gut carcinoid tumors. Most of the cases are thought to secrete such low amounts of hormones that it causes no clinical symptoms, and hormonal, hypersecretory states cannot be detected.[11]

In the present report, only a slight increase in serum serotonin levels occurred without any increase in urinary levels of its metabolites (5-HIAA). This is consistent with the benign behavior in the patient in the study, as the tumors become symptomatic only when hepatic metastases occur, which manifests as classic carcinoid syndrome. It is not clear whether such behavior can be attributed to a benign tumor alone or to an early-stage malignant tumor too. In classic histological terminology, carcinoid lesions are widely regarded as malignant neoplasms.[10,12] However, there are no precise histological criteria to distinguish benign from malignant carcinoid or the carcinoid with metastatic potential. The possibility of a cure in these patients is directly related to an early diagnosis. Unfortunately, as these lesions are asymptomatic or have non-specific clinical manifestations, as in this case, the diagnosis is often delayed. The most frequent symptoms associated with pancreatic carcinoid tumors are abdominal pain (66%) and diarrhea (52%), related to intestinal hypermotility.[7] In some reports,[13–16] pancreatitis seemed to be the consequence of the ductal obstruction by the tumor, while in one report[7] a recurrent pancreatitis was present for more than 10 years before the onset of the first symptoms attributed to a carcinoid. The pathogenesis of the abdominal pain in the patient in this study is difficult to ascertain, as no associated pancreatitis, pancreatic duct dilatation, or neural invasion were detected at the pathological examination. It was suspected that symptoms in the patient might be related to functional or transient events in the intestine or in the pancreatic duct due to episodic humoral or enzymatic secretions by the tumor. This is supported by the intermittent nature of the abdominal pain and the ultrasonographic finding of pancreatic duct dilatation at the first instance, which was not detected on subsequent examinations.

Endoscopic ultrasonography is a useful test for detecting and precisely localizing a tumor within the pancreas.[17] Somatostatin receptor scintigraphy with ^{111}Indium-labeled pentreotide is useful in confirming the neuroendocrine mass and excluding distant metastases.[18] Both these investigations could successfully diagnose and localize the carcinoid tumor in the patient. More extensive application of these two investigations in clinical practice may result in early detection of neuroendocrine tumors even in patients with no or only non-specific complaints.

Meanwhile, one should be aware of the existence of pancreatic carcinoid tumors. For the tumors limited to the pancreas and with no evidence of distant metastases, a radical resection with lymphadenectomy can result in a precise histological characterization of tumor and detection of occult lymph node metastases.[19] Resection at this stage may be curative. ■

Republished from World Journal of Surgical Oncology *2004, 2:3 doi:10.1186/1477-7819-2-3*

10. Williams E D and Sandler M, "The classification of carcinoid tumours", Lancet *(1963), 1: pp. 238–239.*
11. Creutzfeldt W and Stockmann F., "Carcinoids and carcinoid syndrome", Am. J. Med. *(1987), 82: pp. 4–16.*
12. Oberndorfer S, "Karzinoide tumoren des dunndarms", Frankf. Z. Pathol. *(1907), 1: pp. 426–429.*
13. Patchefsky A S, Solit R, Phillips L D, Craddock M, Harrer M V, Cohn H E and Kowlessar O D, "Hydroxyindole-producing tumours of the pancreas, carcinoid-islet cell tumour and oat cell carcinoma", Ann. Int. Med. *(1972), 77: pp. 53–61.*
14. Patchenfsky A S, Gordon G, Harrer W V and Hoch W S, "Carcinoid tumour of the pancreas. Ultrastructural observations of a lymph node metastasis and comparison with bronchial carcinoid", Cancer *(1974), 33: pp. 1,349–1,354.*
15. Nagai E, Yamaguchi K, Hashimoto H and Sakurai T., "Carcinoid tumour of the pancreas with obstructive pancreatitis", M. J. Gastroenterol *(1992), 87: pp. 361–364.*
16. Taidi C, Soyer P, Barge J, Amouyal P and Levesque M., "Tumeur carcinoide primitive du pancreas", J. Radiol. *(1993), 74: pp. 347–350.*
17. Rosch T, Lightdale C J, Botet J F, Boyce G A, Sivak M V Jr, Yasuda K, Heyder N, Palazzo L, Dancygier H, Schusdziarra V et al., "Localisation of pancreatic endocrine tumours by endoscopic untrasonography", N. Engl. J. Med. *(1992), 326: pp. 1,721–1726.*
18. Kisker O, Bartsch D, Weinel R J, Joseph K, Welcke U H, Zaraca F and Rothmund M, "The value of somatostatin-receptor scintigraphy in newly diagnosed endocrine gastroenteropancreatic tumours", J. Am. Coll. Surg. *(1997), 184: pp. 487–492.*
19. Jaffe B M, "Surgery for gut hormone-producing tumours", Am. J. Med. *(1987), 82 (Suppl 5B): pp. 68–76.*