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

**Introduction**

Although carcinoid tumors are the most frequently occurring neuroendocrine tumors, their pancreatic localization is exceedingly rare, and often accidental. In the largest published series of 8,305 cases of carcinoid tumors by Modlin and Sandor, 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. 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. In contrast, there are pancreatic carcinomas with neuroendocrine characteristics and carcinoid-like symptoms. 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, 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. 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, and 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 phlebitis 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).
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

AT THE FIRST SIGN OF CARCINOID SYNDROME...

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Sandostatin LAR® Depot
(Octreotide Acetate for Injectable Suspension)
The Power of Control. Made Easy.

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References:

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**Sandostatin LAR® Depot** (octreotide acetate for injectable suspension)

**In no—**

**INDICATIONS AND USAGE:** Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is indicated for the treatment of patients with acromegaly who, because of the size of the tumor or the patient's clinical status, are not surgical candidates and have had an inadequate therapeutic response to conventional therapy (see PRECAUTIONS). Sandostatin LAR® Depot is not indicated for the treatment of patients with carcinoid syndrome (see PRECAUTIONS).

**CONTRAINDICATIONS:** Pseudohyperparathyroidism (plasma calcium levels greater than 12 mg/dL) in patients with pituitary tumors is a contraindication to treatment with Sandostatin LAR® Depot. The physician should keep in mind that patients with these tumors should be monitored carefully for evidence of hyperparathyroidism. Gastrointestinal disturbances and diarrhea may also occur in patients who have been treated with Sandostatin LAR® Depot for more than 1 year. Multicentric reticulohistiocytosis (see CONTRAINDICATIONS).

**ADVERSE REACTIONS:** Sandostatin LAR® Depot is not indicated for the treatment of the severe diarrhea and flushing episodes associated with carcinoid tumors in patients who have initial treatment with Sandostatin LAR® Depot has been shown to be successful (see PRECAUTIONS).

**Vascular Access:** Sandostatin LAR® Depot has been formulated for long-term subcutaneous administration in patients who have had an inadequate therapeutic response to conventional therapy (see PRECAUTIONS). Sandostatin LAR® Depot is not indicated for the treatment of patients with carcinoid syndrome (see PRECAUTIONS).

**PRECAUTIONS:** Sandostatin LAR® Depot therapy is being studied in patients with a variety of other disorders, including acromegaly, Cushing’s disease, and various carcinoid syndromes. The following adverse reactions were observed during clinical trials with Sandostatin LAR® Depot in patients with acromegaly. Sandostatin LAR® Depot has been shown to be effective in this population (see INDICATIONS AND USAGE).

**Information for Patients:** In acromegalic patients who received Sandostatin® Injection for up to 16 months, developed new clinical laboratories including gastrin, duodenal ulcer. New lesions in 20% of patients were noted.

**Gastrointestinal:** In patients treated with Sandostatin LAR® Depot, diarrhea is the most common gastrointestinal adverse event. In clinical trials with Sandostatin LAR® Depot (primarily patients with carcinoid syndrome), diarrhea was reported in 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

**Cardiovascular:** In acromegalic patients who received Sandostatin® Injection, 12% developed biochemical hypothyroidism, 8% developed hypothyroidism, and 2% developed hypothyroidism. In patients receiving Sandostatin LAR® Depot, hypothyroidism was uncommon. The vast majority of these events were mild-to-moderate in severity.

**Hypoglycemia:** In acromegalic patients treated with either Sandostatin® Injection or Sandostatin LAR® Depot, hypoglycemia was uncommon. In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported. The hypoglycemia or hyperglycemia which occurs during octreotide therapy is usually mild, but may result in death.

**Drug Interactions:** General: Patients receiving Sandostatin LAR® Depot for up to 1 year did not appear to be related to age, sex or dose but was related to duration of exposure. No significant differences were observed in clinical trials with Sandostatin LAR® Depot in patients with acromegaly.

**Hematologic:** The most common adverse reactions are gastrointestinal. The overall incidence of the most frequent adverse events is shown in clinical trials of Sandostatin LAR® Depot. The most frequent adverse events are shown in Table 4.

**Table 4**

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<td>50 (83.3)</td>
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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.

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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 hypoechoic 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 111Indium 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 lymphadenectomy 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.

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. Their incidence varies from 2.1 per 100,000 population per year to 8.4 per 100,000 population per year. 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

A Primary Pancreatic Carcinoid Tumor with Unusual Clinical Complaints

classified into fore-gut carcinoid (respiratory tract, pancreas, stomach, proximal duodenum), mid-gut carcinoid (jejenum, ileum, appendix, Meckel’s diverticulum, ascending colon), and hind-gut (transverse and descending colon, rectum) carcinoid tumors. 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. 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. In some reports,11-13 pancreatistis seemed to be the consequence of the ductal obstruction by the tumor, while in one report7 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. Somatostatin receptor scintigraphy with 111Indium-labeled pentetreotide is useful in confirming the neuroendocrine mass and excluding distant metastases. 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 metastasis. Resection at this stage may be curative.

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