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CLINICAL NOTE

Long-standing malignant pancreatic carcinoid treated with octreotide

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ABSTRACT

A male presented with a metastatic, plasma serotonin-secreting (high 5-HIAA in urine), malignant pancreatic carcinoid with a carcinoid-like syndrome, and was assessed using ultrasounds (US), computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS) and Octreoscan; he sequentially received chemotherapy, interferon and octreotide, with long-term, 12-year survival after diagnosis. Given this unusual case, the second reported in our country, the overall literature is reviewed.

Key words: Pancreatic carcinoid. Serotoninoma. Apudoma or neuroendocrine pancreatic tumor. Serotonin. 5-Hydroxyndoleacetic acid (5-HIAA). Octreotide.

RESUMEN

Se presenta un varón con un carcinoide pancreático maligno, con metástasis, secretor de serotonina plasmática (5-HIAA urinario elevado) con síndrome carcinoide-like, evaluado mediante ecografía (US), tomografía computarizada (TAC), resonancia magnética (RM), ultrasonografía endoscópica (USE) y Octreoscan, tratado con quimioterapia, Interferón y Octeotrida, de forma secuencial, con supervivencia prolongada de 12 años después del diagnóstico.

A propósito de este caso inusual, el segundo publicado desde nuestro país, se revisa la literatura mundial.

Palabras clave: Carcinoide pancreático. Serotoninoma. Apudoma o tumor neuroendocrino pancreático. Serotonina. Ácido 5-hidroxindolacético (5-HIAA). Octeotrida.

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INTRODUCCIÓN

Carcinoid tumors (CTs) represent the most common neuroendocrine tumors (NETs). They are usually located in the thorax and gastrointestinal tract (1); their location within the biliary system (common bile duct), papilla and pancreas is exceptional. Pancreatic CTs are usually malignant (2) and have a poorer prognosis. The rate of pancreatic carcinoids is likely lower than 1% of all carcinoids. We report the case of an Octreoscan-positive malignant pancreatic CTs with metastases and carcinoid-like syndrome that was treated with interferon (3) and octreotide (4), and showed prolonged survival for over 10 years.

CASE REPORT

A 53-year-old male in 1985, smoker, suffering from pain and diarrhea for the last six years and potential chronic pancreatic disease, underwent laparotomy because of a pancreatic growth in the body and uncinate process (biopsy: pancreatic carcinoid) and a second mass at the root of the mesocolon. Following the procedure, through 1996, he kept suffering from abdominal pain, chronic diarrhea, steatorrhea, tearing, and mild flush (carcinoid-like syndrome). He also developed

cholelithiasis, skin pigmentation and exophthalmos. He died 12 years after diagnosis and 18 years after initial symptoms from ascites, overall metastatic disease, and multiple organ failure. Following laparotomy, he received chemotherapy with streptozotocin plus 5-fluorouracil (STZ + 5-FU) for 6 weeks, octreotide and interferon alfa-2b.

Interferon alfa-2b at 3 MU/day/3 days (induction) and at 5 MU three times a week for 5 months resulted in no tumor or biochemical response. The patient had to discontinue therapy because of mild flu-like syndrome, leukopenia, and low platelet count (3). Octrotide as chronic therapy at 50-100 μg/12 hrs resulted in clinical and biochemical responses, although, as adverse event, he developed BL and repeat biliary colics (4).

Laboratory tests were normal except for hypocholesterolemia. Hyperthyroidism, hemochromatosis, and Cushing syndrome were ruled out. Hormonal tests: serotonin, 2125 ng/ml (62-159). Gastrin, 29 pg/ml (< 100). Insulin, 11 μU/ml (5-20). Glucagon, 117 and 149 pg/ml (50-250). VIP, 6 pmol/l (< 30). Somatostatin (SMS), 20 pg/ml (10-25). Neuron-specific enolase (NSE), 2.2 ng/ml (< 13). Prostaglandin (PGE), < 4.3 pg/ml. ACTH, 22 pg/ml (N < 70). CEA, 1.5 ng/ml (< 6). Catecholamines and metanephrines in 24-h urine were normal. Urine 5-HIAA (N: < 12 mg/24 hr), 44 mg/24 hr (1986). Urine 5-HIAA (N: < 10 mg/24 hr), 119.7 mg/24 hr. Serotonin, 1100 ng/ml (50-300) (1992). Urine 5-HIAA (N: < 10 mg/24 hr), 147.8 mg/24 hr at baseline; at 2 months 66.6 and at 1 year 6 mg/24 hr post-octreotide for 12 months at the above doses. Fat in stool: in 1988, > 8 gr/24 hr; 9.8 gr/24 hr. In 1992, 20 gr/100 gr weight and day; 38 gr/100 gr weight and day. Fat in stool turned to normal amount after oral administration of pancreatic enzymes (5).

Imaging (Figs. 1-4): Computerized tomography (CT) (1985) and ultrasound (US): hypodense, hypoechoic 2-cm mass in the pancreas. Liver metastasis (5

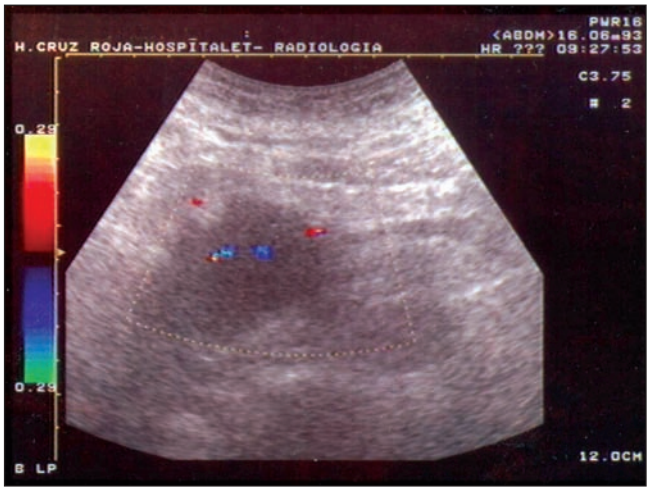

Fig. 1. US: Sagittal and transverse sonographic sections (3.5 MHz) of this hypoechogenic pancreatic tumor.

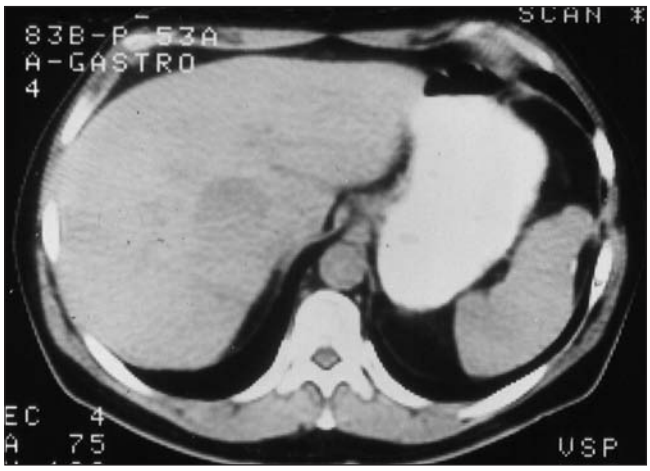

Fig. 2. CT: Hypodense liver metastasis.

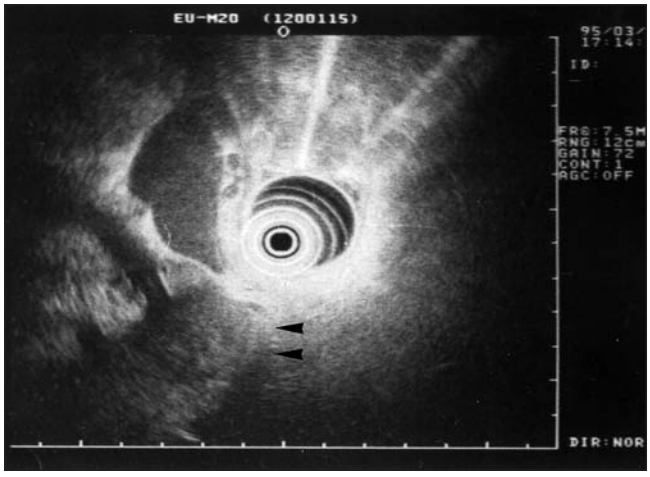

Fig. 3. EUS: A pancreatic carcinoid (below, two arrows) compressing a widely dilated bile duct with lithogenic bile and biliary mud, as well as the portal vein.

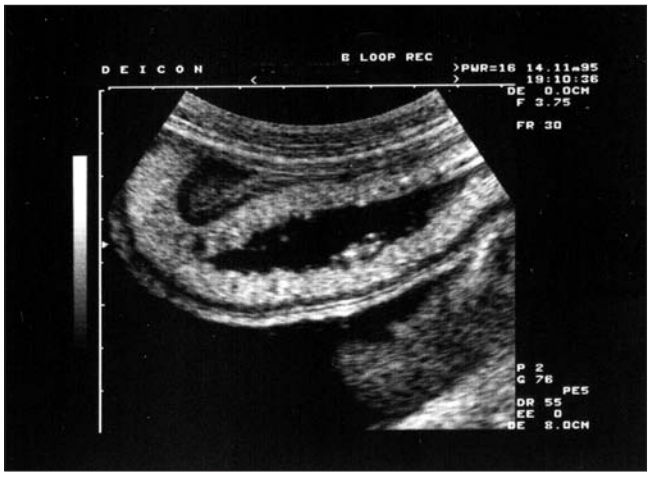

Fig. 4. US: Abdominal section (3.75 MHz) showing ascites, mesenteric infiltration, and intestinal wall hypertrophy at the expense of the mucosa and submucosa. The dual muscularis propria and serosal layers are finely delimited as though with EUS.

cm) at the caudate with mild contrast uptake. Magnetic resonance imagen: same diagnosis. Endoscopic ultrasound (EUS) (1987): heart valve calcification, liver metastasis, no pancreatic mass can be detected because patient was intolerant to examination. Cranial CT: Normal. CT (1989, 1992): Two metastases of 1 and 8 cm in the right and caudate lobes; hypodense growth in head-body. All this images were greater in size as compared to previous workup in 1985. US (1990): Two echogenic metastases of 1 and 6 cm; BL; hypoechogenic growth 26-30 mm in size. Color Doppler US (1993), non vascularized echogenic metastases. No portal thrombosis. Octreoscan (1995), positive for liver metastasis and pancreatic tumor (hyperactive). EUS (1995): BL and hypoechogenic pancreatic mass dilating the common bile duct and portal vein. US (1995), ascites, BL, metastases, 39 and 65 mm in size, and pancreas tumor greater than 30 mm that was dilating bile duct system and Wirsung (3.6 mm). Thickened intestinal wall. Bowel follow-through (1995): mesenteritis.

DISCUSSION

Formerly, the term pancreatic carcinoid tumor was considered similar to pancreatic islet cell tumor or to pancreatic neuroendocrine tumor. Currently, pancreatic carcinoid is considered the pancreatic serotoninome or endocrine tumor of the pancreas secreting serotonine. The first reported cases of pancreatic carcinoid date back to the 1960s and 70s. The first case ever reported is likely the one by Pataky et al. in 1959 (6). Through 1963, only 13 cases had been reported (7), and until 1983, we reviewed 25 cases. Patchefsky et al. (8) reported 4 cases of endocrine pancreatic tumors with high urine 5-HIAA. In 1986, the first case associated with multiple endocrine neoplasm (MEN-1) was reported (9), though cases with multiple hormone secretion (MHS) had been previously found.

Clinical manifestations of pancreatic carcinoid include abdominal pain, diarrhea, and weight loss, with typical CS from 5-hydroxytryptamine (serotonin) production or atypical CS from serotonin precursor 5-hydroxytryptophan. Cases had been reported that caused acute or chronic pancreatitis (10,11). Our patient presented with all these abnormalities in addition of steatorrhea from potential exocrine pancreatic deficiency that was treated with oral pancreatic enzymes (5); exocrine pancreatic insufficiency has also been associated with gastrinoma, somatostatinoma (12) and carcinoid (13).

In 1996 (14), in connection with a case, 29 patients reported between 1966 and 1995 were reviewed. Tumors had a mean diameter of 4 cm, many had multiple hormone secretion with atypical carcinoid syndrome, there was flush in only 34%, and 69% were malignant. High urine 5-HIAA was seen in 85% of cases, and 100% showed serotonin-positive immunocytochemistry. In 1998 (16), two additional cases are reported and 43 patients are reviewed. Eighty eight percent of cases were malignant with poor prognosis. Modlin and Sandor (15) estimated US frequency as 0.55%, 0.58% of all carcinoid tumors, with 5-year survival between 34% (17) and 37.5% (18). Soga (19) reviewed 156/11.343 cases of carcinoid (1.4%) and compared them to 165 reported worldwide. Most (66.7%) tumors were malignant and 23% of them had CS; 93% showed serotonin-positive immunohistochemistry, and the 5-year survival was low at 29%. Waisberg et al. (20) estimated its frequency below 1%, being a rarity in children and young adults. In our recently reported series of carcinoids, frequency is 2% (21). Bilimoria et al., in 2007 (22), estimated frequency to be 7.9% of pancreatic endocrine tumors (PETs). They mostly presented at a mean age of 63 years in Caucasian individuals of both sexes, and metastases developed in 63.5%. A recent Chinese series reported 8 cases in 2009 (23) with a mean age of 37 years (range 8 to 52). Fifty percent of patients were females; radical surgery was performed in 62.5% with a good outcome in four, despite the fact that 37.5% had liver mestastases and metastatic disease was unveiled in 50%.

Location is usually established by using US/CT/MRI (24-27), but some cases have been localized with EUS (28-30) and Octreoscan (31). The exact role PET-CT may play is currently unknown. On ultrasonograms, pancreatic carcinoids are usually hypoechogenic and, when located in the head, originate in bile system dilation, as was our case. CT shows hypodense, homogeneous growths when small, or heterogeneous masses with cystic necrosis areas when large (25). In our case, diagnostic images were taken using US/CT/MRI/EUS/Octreoscan (Figs. 1-4). The last sonogram identified dilation of the common pancreatic duct (Wirsung), as recently reported (26,27), as well as thickened intestinal wall and ascites.

Ideal therapy consists of surgical resection with curative intent, which at times is not feasible because of malignity and frequency of metastases. However good response rates have been reported with octreotide (32), as it was in our case. Chemo-radiotherapy, primary tumor resection and liver transplantation are option in cases of metastatic disease (33). Chemoembolization (34) and medical management with somatostatin analogs and interferon are also useful, as is the treatment with In111-DTPA (35,36). Our patient clinically and biochemically responded to acute and chronic therapy with octreotide.

Over 200 cases of pancreatic carcinoids have most likely been reported as of today; the following ensues from a literature review (Table I) (16): a) pancreatic carcinoid or serotoninoma secretes and releases sero-

Table I. Literature summary

Pataky (6)		First case reported
Hiller (7)	1959-1963	13 cases reviewed
Patchefsky (8)		4 cases reported
Varas	1963-1983	25 cases reviewed
Maurer (14)	1966-1995	29 cases reviewed and 1 new case reported
Mao (16)	through 1998	43 cases including two new ones
Modlin (17)	1950-1999	79 cases reviewed in USA
Soga (19)	2005	156 cases reviewed in Japan *vs.* 165 worldwide
Pérez-Fidalgo (33)	2006	1st case report in our country
He (23)	2009	8 cases reported and reviewed

tonin (5-HIAA in urine), since it is made up of EC cells (argyrophilia) within the pancreas, with positive immunohistochemistry for said hormone; b) tumors are malignant in about 70% of cases, and present with either typical or atypical CS (fewer than 50%) as well as a triad of abdominal pain, diarrhea, and weight loss; c) survival at 5 years is low, around 30%, but may respond to somatostatin analogs and radical surgery; d) frequency is around 1% of all carcinoids, and 10-year survival is 10% (35) because of high malignant potential (36); e) they may be associated with MHS, MEN-1 (9), and gastroduodenal carcinoids (37); and f) in contrast to pancreatic carcinoids, carcinoids in the common bile duct and minor papilla are extremely rare (8 cases reported), and those of the papilla are rare (70 cases reported) (38).

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