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Acute Pancreatitis Secondary to Pancreatic Neuroendocrine Tumours

Pilar Griñó[1], Juan Martínez[1], Emilio Griñó[1], Fernando Carnicer[1], Sergio Alonso[2], Helena Pérez-Berenguer[3], Miguel Pérez-Mateo[1]

[1]Department of Gastroenterology, [2]Service of Radiodiagnosis, [3]Service of Pathology, Hospital General Universitario de Alicante. Alicante, Spain

ABSTRACT

Context Pancreatic neoplasms are an uncommon aetiology of acute pancreatitis. Pancreatic neuroendocrine tumours are a rare subgroup of pancreatic neoplasms.

Case report We report on three patients having acute pancreatitis secondary to pancreatic neuroendocrine tumours, one of them with severe pancreatitis, and review the published cases up to now.
Only 22 patients with acute pancreatitis secondary to pancreatic neuroendocrine tumours have been reported (including the present cases). Most of these cases were of non-functioning neoplasms and the course of the pancreatitis tended to be mild. In the most recent reports and in the present cases, the initial diagnostic method was CT scan. Less than half had metastases when the tumour was diagnosed and mortality from these neoplasms reached approximately 50%.

Conclusions Pancreatic neuroendocrine tumours can cause acute pancreatitis even in patients under 50 years of age. On many occasions, the tumours are non-functioning; therefore, acute pancreatitis may be the first clinical symptom. Consequently, faced with acute pancreatitis of unknown origin, a non-functioning neuroendocrine tumour should be ruled out.

INTRODUCTION

Pancreatic neuroendocrine tumours (PNT) represent less than 10% of all pancreatic tumours [1]. They usually manifest few symptoms, except when there is a hormone syndrome associated with them; therefore, they are diagnosed at an advanced stage [2].
Furthermore, pancreatic tumours are a known but uncommon cause of acute pancreatitis [3]. We report on three patients having acute pancreatitis secondary to PNT. One of them (Case 1) was previously reported [4].

CASE REPORT

Case 1

A 73 year old woman was admitted to our hospital complaining of intense epigastric pain. On admission, she had hyperamylasemia (820 U/L) and hyperlipasemia (447 U/L). Abdominal ultrasonography showed the presence of perihepatic fluid, but the pancreas could not be seen. There were no gallstones. On abdominal CT scan, the pancreas was seen to be enlarged, particularly the tail. There were large peripancreatic collections of fluid at this level, but no signs of necrosis. The main pancreatic duct was not enlarged on either ultrasonography or CT. The outcome was poor, with progressive worsening, fever, anaemia and finally organ failure. Surgical treatment was therefore indicated four weeks

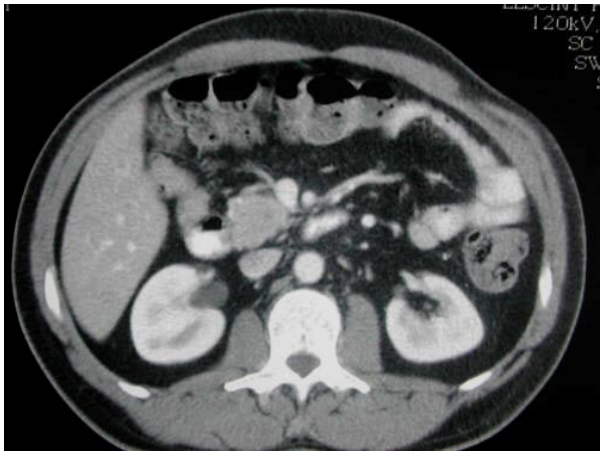

Figure 1. Helical CT aspect of a pancreatic neuroendocrine tumour: hyperdense mass in uncinate process.

after hospital admission. At surgery, fluid was drained, and a previously undetected mass seen in the tail of the pancreas, surrounded by extensive areas of tissue, was excised. The patient died of multi-organ failure a few days post-operatively. Histological study of the tissue removed showed a neoplasm with neuro-endocrine features which stained positively with an immuno-histochemical technique for synaptophysin and enolase but was negative for hormones.

Case 2

A 43 year old man was admitted to our hospital with epigastric pain of sudden onset. Two years previously, he had had a cholecystectomy for biliary colic. On admission, he was found to have elevated serum amylase and lipase levels (1,017 U/L and 2,137 U/L, respectively). Abdominal ultrasonography was normal. Subsequently, a helical CT scan of the abdomen showed a hyperdense mass, 2 cm in diameter, at the level of the pancreatic uncinate process (Figure 1). The main pancreatic duct was not dilated. Therefore, percutaneous fine needle aspiration (FNA) was done, which led to the diagnosis of a tumour having neuro-endocrine characteristics. The peripheral blood levels of insulin, parathyroid hormone (PTH), gastrin, vasoactive intestinal peptide (VIP) and somatostatin were normal, while the level of glucagon was slightly elevated (238 pg/mL). Magnetic resonance (MR) confirmed the presence of a tumour located in the head of the pancreas and a 1cm nodule in the liver in the fourth hepatic segment, which had not been previously detected (Figure 2). Somatostatin receptor scintigraphy was normal. Subsequently, it was decided to perform surgical resection in two stages. Initially, a cephalic duodenopancreatectomy was done and then, some months later, the liver metastasis was resected. Histological examination of the two resected specimens confirmed the preoperative diagnosis: neoplastic proliferation, with cells which tended to be grouped together in solid nests or in an alveolar or trabeculated manner. An immunohistochemical study showed that the tumour cells stained positive for cytokeratins and synaptophysins but negative for gastrin, VIP, ACTH and insulin, weakly positive for glucagons and over 20% of the cells positive for somatostatin. All this was compatible with a neuro-endocrine tumour. One year later, a single liver metastasis was detected on MR in hepatic segment six. This was surgically resected. Subsequently, three new metastases developed and a liver transplant was indicated. However, the patient died immediately post-operatively due to technical complications.

Case 3

A 44 year old man was admitted complaining of intense abdominal pain. On admission, he

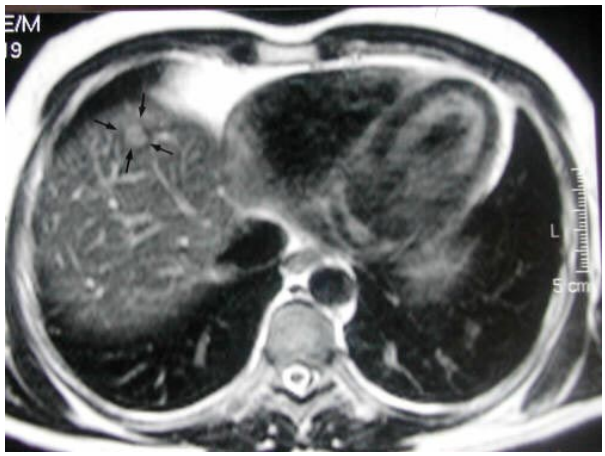

Figure 2. Small liver metastasis (4th segment) of a pancreatic neuroendocrine tumour on a T2 weighting MR imaging (arrows).

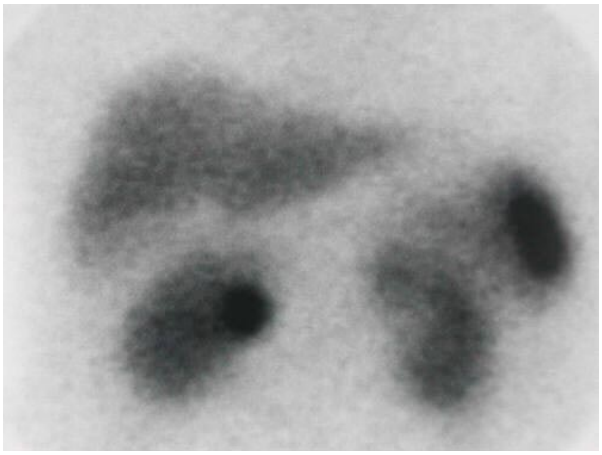

Figure 3. Scintigraphic aspect of a pancreatic neuroendocrine tumour in the head of the pancreas

had hyperamylasemia (1,591 U/L). The abdominal ultrasonography was normal. A helical CT scan showed a hyperdense mass of 2.2 cm in the head of the pancreas. The main pancreatic duct was not enlarged. The FNA of the pancreatic mass showed the presence of neuroendocrine cells. A study of the peripheral blood hormones showed the levels of insulin, gastrin, VIP, glucagon, PTH and somatostatin to be normal. Somatostatin receptor scintigraphy showed a pancreatic neoplasm, with no evidence of local or distant spread (Figure 3). A cephalic duodeno-pancreatectomy was done. Histological study of the surgical specimen confirmed the presence of a tumour whose architecture was mainly trabecular, with cells of uniform size and morphology similar to that of the islet cells, occasional mitoses and the absence of vascular infiltration and necrosis. An immunohistochemical study was positive for neuro-endocrine markers (synaptophysin and enolase) but no hormones were shown. The patient died after acute necrotizing pancreatitis occurred post-operatively.

The characteristics of the three patients are summarized in Table 1.

DISCUSSION

In Spain, as in most western countries, gallstones and alcohol intake are the most common causes of acute pancreatitis [5]. Pancreatic neoplasms are a known but uncommon cause of acute pancreatitis. The exact mechanism whereby a tumour may cause acute pancreatitis is not clear. It may be due to obstruction of the duct, ischaemia secondary to vascular occlusion due to the malignant cells or to the activation of pancreatic enzymes due to tumour cells [3]. PNTs account for a small proportion of such tumours. There are neoplasms which may cause chronic pancreatitis, either due to associated hormone activity (such as the Zollinger-Ellison syndrome) [6] or directly due to an obstructive mechanism [7, 8]. However, the association between acute pancreatitis and PNT is uncommon. Considering only patients with abdominal pain and increased pancreatic enzymes and/or acute signs on imaging techniques (without evidence of chronic pancreatitis in histological studies), up to now, only twenty cases of acute pancreatitis induced by PNT have been described [4, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. We present two new cases together with one previously reported (Case 1) [4]. The pathophysiology of acute pancreatitis in PNTs is attributed to several mechanisms. Some tumours release hormones which may be responsible for acute pancreatitis (i.e., hypercalcaemia secondary to parathyroid hormone). However, most PNTs produce mechanical obstruction of the pancreatic ducts, regardless of whether the tumour is functioning or non-functioning [9]. All our patients had non-functioning PNTs. Although there was no evidence of main pancreatic duct obstruction on imaging methods (ultrasonography, CT scan, MR),

Table 1. Characteristics of patients included in the present series.

Sex	Age	Localization	Type	Diagnosis	Metastases	AP Severity	Survival	Ref.
Female	73	Tail	NF	Surgery	No	Severe	No	[4]
Male	43	Head	NF	CT, MR	Liver	Mild	No	-
Male	44	Head	NF	CT, MR, Scintigraphy	No	Mild	No	-

AP: acute pancreatitis; NF: non functioning

pancreatography was not possible using either MRCP or ERCP. Therefore, mechanical obstruction could not be ruled out. Table 2 shows the characteristics of the previously reported patients with acute pancreatitis secondary to PNT. Sex distribution is homogeneous (8 males, 7 females, 4 non-specified). Most patients were young when the tumour was diagnosed, although one of our patients is the oldest in the series (73 years old).

In all cases but one (gastrinoma) [13] the tumours were considered to be non-functioning. The tumour, which was previously unsuspected, probably appeared as a result of it causing acute pancreatitis. In this regard, at least nine patients had distant or regional metastases when the tumour was diagnosed, suggesting a delayed diagnosis due to this silent evolution.

The course of the acute pancreatitis associated with these tumours tends to be mild, without the development of complications. Two patients suffered severe acute pancreatitis, one of them developed a pseudocyst [16] and the other, one of our cases, developed severe acute pancreatitis with multi-organ failure and died. However, the course of the illness due to the tumour itself tends to be more varied, as is shown in Table 2. In four patients, death occurred as a direct result of the tumour or its treatment. In our cases, death was a direct consequence of the tumour due to severe acute pancreatitis and, in the others, death was secondary to surgery (post-surgical severe acute pancreatitis and technical complications of liver transplant).

In one third of the cases, tumours were found in the head of the pancreas. In no case, however, did the tumour cause obstructive jaundice, as opposed to what may be expected in cases of adenocarcinoma of the head of the pancreas. The relatively slow growth of these tumours could be an explanation. Tumours were also common in the tail of the pancreas and only two patients had involvement at distant sites.

Diagnosis of the site of these tumours is made

Table 2. Reported patients with acute pancreatitis secondary to pancreatic neuroendocrine tumours.

Sex	Age	Localization	Type	Diagnosis	Metastases	AP Severity	Survival	Ref.
Male	56	Whole	NF	Surgery	Kidneys, Gallbladder, Thyroid, Adrenal glands	Mild	No	[10]
Female	52	Body	NF	Surgery	Liver	Mild	Yes	[11]
Female	20	Tail	NF	US	No	Mild	Yes	[12]
Male	56	NA	Gastrinoma	NA	Liver	Mild	Yes	[13]
NA	NA	NA	NF	NA	NA	Mild	NA	[14]
NA	NA	NA	NF	NA	NA	Mild	NA	[14]
Male	50	Head	NA	ERCP , Surgery	Lymphatic nodes	Mild	Yes	[15]
Female	63	Head	NA	CT, ERCP	No	Mild	No	[15]
Male	46	Head	NA	ERCP, Surgery	Bone	Mild	Yes	[15]
Male	58	Head	NA	CT, ERCP	Lymphatic nodes	Mild	Yes	[15]
Male	53	Tail	NF	ERCP, CT	No	Severe	No	[16]
NA	NA	NA	NF	NA	Liver	Mild	NA	[17]
NA	NA	NA	NF	NA	No	Mild	NA	[17]
Female	38	Body	NF	ERCP, Surgery	No	Mild	Yes	[18]
Female	26	Body	NF	ERCP, Surgery	No	Mild	Yes	[18]
Female	49	Tail	NF	ERCP	Lymphatic nodes	Mild	Yes	[19]
Female	57	Tail	NF	ERCP	No	Mild	Yes	[19]
Male	41	Head	NF	CT, US	No	Mild	Yes	[20]
Male	48	Tail	NF	CT, Laparoscopic-US	Liver	Mild	No	[21]

AP: acute pancreatitis; NA: not available; NF: non functioning; US: ultrasonography

using imaging techniques. Classically, ultrasonography, CT and ERCP have been used. However, the results are not really satisfactory since there may be up to 60% of false negatives [22, 23]. In our cases, no tumour was detected on ultrasonography. CT only showed neoplasms in two cases, namely, in those in which helicoidal CT, which gives better resolution in pancreatic tumours, was used. In the other case, apart from conventional CT being used, the presence of a considerable amount of peritumoural inflammatory tissue may have made it impossible to detect the tumour using this technique. MR may improve the diagnosis of pancreatic tumours, regarding both their site and extension [24]. In one of our patients, MR was the technique which permitted the detection of liver metastases which had not been diagnosed on either ultrasonography or helicoidal CT scan. At present, endoscopic ultrasonography (EUS) and somatostatin receptor scintigraphy are the techniques of choice for evaluation of the size and extent of these tumours, with good results and great sensitivity [25, 26]. The existence of somatostatin receptors, a common event in neuroendocrine tumours, enhances the diagnostic accuracy of scintigraphy [27]. However, although somatostatin receptor scintigraphy was used on two patients, findings were positive in only one.

In general, treatment of these neoplasms is based on control of the hormone syndrome associated with it (if present) and resection of the tumour when it is localized [28, 29], as was done in our three cases. Unfortunately, two of them died as a consequence of surgery. The other patient developed hepatic metastases. The liver is the main target organ for metastases. Several therapies have been described regarding hepatic metastases. They include resective surgery [30], ablative methods such as thermal ablation [31, 32, 33] or liver transplant [34, 35]. In our patient, initially the metastasis located in hepatic segment 6 was resected, but later new hepatic metastases appeared; therefore, a hepatic transplant was attempted taking into account the absence of any extra-hepatic tumour. However, the patient died immediately after being operated on. Finally, in cases of unresectable tumours, chemotherapy is indicated [28, 36].

In conclusion, although infrequent, pancreatic neuroendocrine tumours can cause acute pancreatitis even in patients under 50 years of age. On many occasions the tumours are non-functioning; therefore, acute pancreatitis can be the first clinical symptom. Consequently, faced with acute pancreatitis of unknown origin, even in young patients, a non-functioning neuroendocrine tumour should be ruled out.

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Abbreviations EUS: endoscopic ultrasonography; FNA: fine needle aspiration; MRCP: magnetic resonance cholangiopancreatography; PNT: pancreatic neuroendocrine tumours

Correspondence
Juan Martínez
Sección de Digestivo
Hospital General Universitario de Alicante
Pintor Baeza s/n
Alicante 03010
Spain
Phone: +34-965-938.345
Fax: +34-965-938.355
E-mail address: martinez_juasem@gva.es

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