Acta Clin Croat 2008; 47:165-170 Case Report

PANCREATIC ENDOCRINE TUMOR OF UNCERTAIN BEHAVIOR: A CASE REPORT

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SUMMARY – Pancreatic endocrine tumors are rare, and among them large non-functioning tumors of uncertain behavior are extremely infrequent. Non-functioning pancreatic endocrine tumors originate from the endocrine part of the pancreas but are not associated with a distinct hormonal syndrome. A rare case is presented of a 49-year-old woman with a well-differentiated endocrine tumor of uncertain behavior that presented with intermittent pain in the epigastrium radiating to the right subcostal region. Computed tomography showed a well-defined and circumscribed solid mass in the pancreas head. The pancreatic mass was surgically removed and submitted for histopathologic analysis. Microscopically, the tumor had relatively uniform cells with oval nuclei that coated trabecular and pseudoglandular structures, which also showed 1 mitosis *per* 10 VVP and proliferation activity measured with Ki67 of less than 2%. A focus of intravascular invasion was seen on one slide. Immunohistochemical analyses for NSE, chromogranin and synapthophysin were positive, which along with its size (over 2 cm in diameter) and reported angioinvasion indicated the diagnosis of pancreatic endocrine tumor of uncertain behavior. Although mostly considered as malignant, large non-functioning pancreatic endocrine tumors can sometimes express benign or uncertain behavior; therefore, a large number of factors should always be considered when determining the biological nature of these tumors.

Key words: *Endocrine gland neoplasms – diagnosis; Endocrine gland neoplasms – surgery; Pancreatic neoplasms – classification; Pancreatic neoplasms – diagnosis; Pancreatic neoplasms – surgery; Case report*

Introduction

All pancreatic endocrine tumors are rare, being estimated at about 5 cases *per* 1 million population *per* year. The tumors show no significant sex predilection and may occur at all ages, with a peak incidence in the 30-60 age groups. Endocrine cells of the pancreas reside in islets, and the adult human pancreatic islet contains multiple types: A (alpha) cell secretes glucagon, B (beta) cell secretes insulin, D (delta) cell secretes somatostatin, D2 (delta-2) cell secretes vasoactive intestinal peptide (VIP), and PP (or F) cell secretes pancreatic polypeptide (PP). Tumors of any of these cells may in fact secrete multiple peptides, serially or simultaneously. The syndromes produced are named after the peptide of predominant symptoms. Thus, endocrine pancreas may produce insulinomas, glucagonomas, somatostatinomas, VIPomas, PPomas, or gastrinomas. These are functioning tumors[1]. Non-functioning (or inactive, clinically silent, non-syndromic) tumors are not associated with a distinct hormonal syndrome. They make around 40% of all pancreatic endocrine tumors[2]. In most cases they become clinically apparent due to their large size, invasion of adjacent organs, or occurrence of metastases. Rarely, they may present as acute pancreatitis. Increasingly, they are incidentally detected on imaging tests like multislice computed tomography (MSCT) or nuclear magnetic resonance (NMR)[3,4].

Non-functioning tumors are generally larger than 2 cm in diameter (often 5 cm or more). Those with diameter of more than 2 cm have an increased risk of malig-

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Received July 7, accepted August 26, 2008

nant behavior and those over 3 cm are usually malignant. A small number of them are well-differentiated tumors showing benign or uncertain behavior; however, the vast majority (approximately 90%-95%) are well-differentiated carcinomas[1]. We report a case of a 49-year-old woman with a well-differentiated endocrine tumor of uncertain behavior that presented with intermittent pain in the epigastrium radiating to the right subcostal region.

Case Report

A 49-year-old woman was referred to our hospital with a six-month history of epigastric pain radiating to the right subcostal region. The patient was without previous history of illness, except for cholecystectomy performed 17 years before. Physical examination showed no palpable mass in the abdominal region. Results of laboratory tests including blood count and biochemical tests were within the normal limits. Multi-slice computed tomography revealed a well-defined and circumscribed solid mass in the pancreas head, which measured 3.5x2 cm, without any other signs of neoplastic infiltration or metastases (Fig. 1). Radiological findings did not show definitive demarcation between the mass and the pancreas, and the possible malignancy could not be ruled out. The patient underwent surgery for resection of the pancreatic mass. On laparotomy, a solid circumscribed tumor was detected in the head of the pancreas, measuring 3.5 cm in diameter (Fig. 2). There was no visual infiltration of the duodenal wall or adjacent organs. Despite this, proximal pancreatoduodenectomy was performed, involving resection of the distal stomach, duodenum and the head of the pancreas *en bloc*. The entire tumor was referred for histopathologic analysis. Grossly, the tumor was solid, well-circumscribed and surrounded with thin capsule; it measured 3.5 cm in largest diameter. Macroscopically, it had a thin capsule of connective tissue. It did not infiltrate the intestine nor was it detected in resection margins of the pancreas. Microscopic examination of the tumor frozen section and paraffin embedded slides stained with hematoxylin-eosin revealed relatively uniform cells with oval nuclei that were coating trabecular and pseudoglandular structures (Fig. 3A). Tumor cells showed 1 mitosis *per* 10 VVP; proliferation activity measured with Ki67 was less than 2%. A focus of intravascular invasion was observed on one slide (Fig. 3B). Immunohistochemical analyses, positive for NSE, chromogranin and synapthophysin, were consistent with pancreatic endocrine tumor. There were no positive lymph nodes in the surrounding adipose tissue. The patient was discharged from the hospital on postoperative day 13; on surgical check up 6 months later, the patient was well and symptom free. The patient has been continuously followed by a surgeon. According to histological, histochemical (PAS) and immunohistochemical findings, along with its size (over 2 cm) and angioinvasion, the tumor correlated with well-differentiated pancreatic endocrine tumors of uncertain behavior, as defined in the 2004 World Health Organization classification of endocrine tumors[1,5] (Table 1).

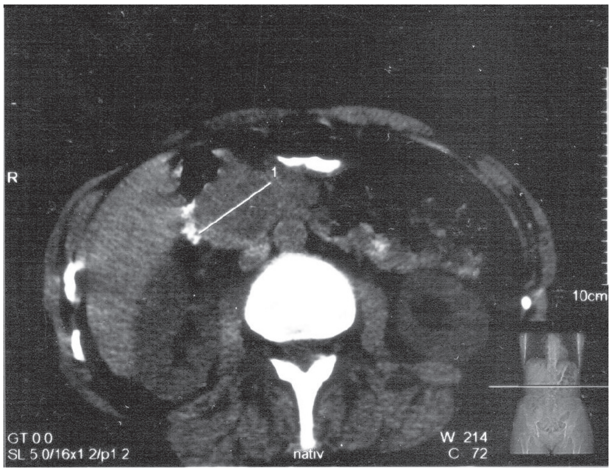

Fig. 1. Computed tomography revealed a well-defined and circumscribed solid mass in the pancreas head.

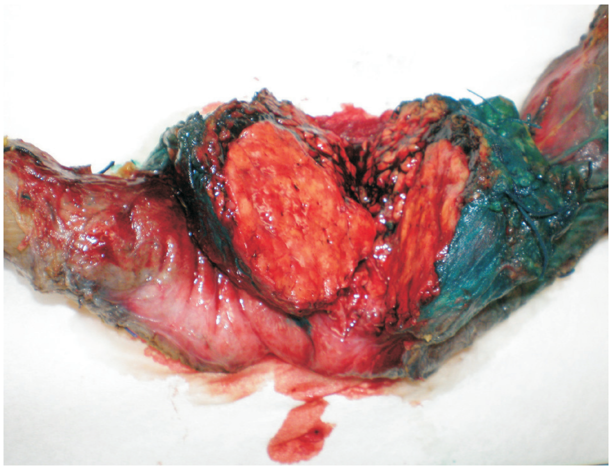

Fig. 2. The head of the pancreas was partially replaced by a yellowish circumscribed tumor measuring 3.5 cm in diameter.

Table 1. Criteria for clinicopathologic classification of pancreatic endocrine tumors

1	*Well-differentiated endocrine tumor*
1.1	'Benign' behavior Confined to the pancreas, non-angioinvasive, no perineural invasion, <2 cm in diameter, <2 mitoses/10 HPF and <2% Ki-67 positive cells
1.2.	Uncertain behaviour Confined to the pancreas and one or more of the following features: ≥2 cm in diameter, 2-10 mitoses/10 HPF, >2% Ki-67 positive cells, angioinvasion, perineural invasion
2	*Well-differentiated endocrine carcinoma* Low grade malignant Gross local invasion and/or metastases
3	*Poorly-differentiated endocrine carcinoma* High grade malignant >10 mitoses/10 HPF

Discussion

Non-functioning tumors are generally larger than 2 cm in diameter (often 5 cm or more). Those with a diameter of more than 2 cm have an increased risk of malignant behavior and those over 3 cm are usually malignant. A small number of them are well-differentiated tumors showing benign or uncertain behavior; however, the vast majority (approximately 90%-95%) are well-differentiated carcinomas[1]. It has been proposed to divide these tumors into prognostic groups based on mitotic rate and necrosis. In a manner reminiscent of stage-by-stage progression of normal gut epithelium to eventual malignancy, tumorigenesis of neuroendocrine cells appears to involve multiple genetic events (mutational activation or inactivation of oncogenes or tumor suppressor genes). For these tumors, the criterion of malignancy is simple: if metastasizing, they are malignant. On hematoxylin and eosin stains, all pancreatic endocrine tumors (including carcinoid tumors of the bowel) look alike. Immunostaining using antibodies to specific hormones allows for identification of the endocrine content of cells[6]. On light microscopy, there are no characteristics discriminating benign from malignant tumors. Some large aggressive tumors may invade adjacent structures and by such action proclaim their malignancy, but most tumors larger than 2 cm are seen as malignant anyway. The final "morpho-functional" classification of an endocrine tumor of the pancreas should take in consideration the following: (1) the clinical syndrome induced by or associated with the tumor; (2) determination of the blood concentration of hormones(s) secreted by the tumor; (3) the size (mass) of the tumor; (4) histologic differentiation and probable biologic behavior of the tumor; (5) the phenotype(s) of various tumor cells; and, if necessary and feasible (6) molecular genetic analysis of the tumor[1]. We found nine non-functioning endocrine tumors of the pancreas larger than 2 cm reported in the English literature. The tumors measured between 3 and 9 cm in largest diameter. In one case, the tumor was defined as benign and in the other cases the tumors were ruled out as malignant. The malignancy factor was local microscopic invasion in three cases, regional lymph node

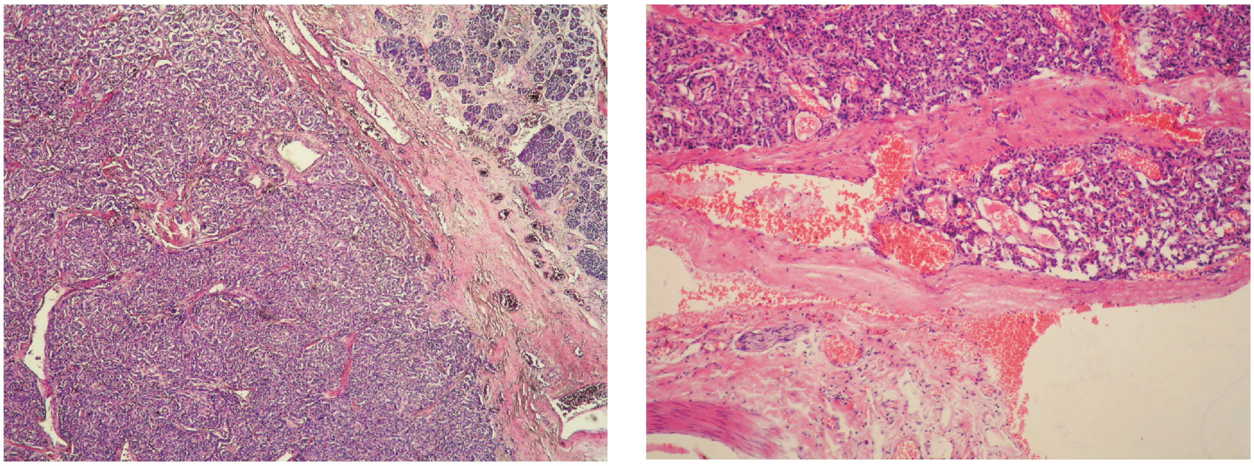

Fig. 3. Microscopic examination showed relatively uniform cells with oval nuclei that were coating trabecular and pseudoglandular structures (left); and the focus of intravascular invasion observed on one slide (right).

involvement in two cases, adjacent organ invasion in one case, and hepatic metastasis in the remaining cases[7-10]. Preoperative diagnosis based on clinical presentation and radiological appearance of non-functioning endocrine tumors of the pancreas is often fundamental to conclude on the benign or malignant nature of these tumors. Histopathologically, all of these tumors involve abnormal cells with some malignant potential. Therefore, it is important to look for clinical and pathologic evidence of malignancy, e.g., metastatic disease, lymph node involvement and vascular invasion. As already stressed, morphologically, in the past 10 years, tumor size has been found to be a good prognostic indicator; larger tumors are more likely to be malignant than smaller ones. However, facing a large tumor, >2 cm in diameter, and in the absence of any other clinical and pathologic evidence of malignancy, histopathologic and immunohistochemical variables should be taken in consideration when determining tumor classification. These variables include: vascular or perineural microinvasion, Ki67 proliferative index $>2\%$, mitotic rate ≥ 2, nuclear atypia, and capsular penetration[5]. Heterogeneity is also an indicator; more areas of necrosis and hemorrhage indicate a greater likelihood of malignancy. Calcification, which is often associated with benign tumors, is an indicator of malignancy in islet cell tumors. Many of the smaller tumors also have malignant potential, but interruption of their natural history by surgical resection prevents the expression of such potential. Complete surgical removal of the tumor is recommended to allow for accurate diagnosis and prevention or resolution of complications[11-13]. The most common complications are obstruction of the biliary duct, duodenal obstruction, gastrointestinal hemorrhage and acute pancreatitis, which has also been described[14,15]. Surgical strategy depends on the size and location of the tumor and the risk of malignancy. Aggressive surgical approach leads to cure in patients with benign pancreatic endocrine tumors. Although long-term cure can only be achieved in a proportion of patients with malignant tumors, significant palliation can be achieved[13]. Long-term clinical follow up is needed to establish definitive biologic nature of the tumor because metastases may develop years after removal of the primary lesion[16,17]. In conclusion, although large non-functioning pancreatic endocrine tumors are mostly considered as malignant, some of them show benign or uncertain behavior. For appropriate classification and prognosis, a number of factors should be taken in consideration such as metastasis, gross invasion, tumor diameter, angioinvasion, perineural invasion, mitosis, necrosis, regional lymph nodes, status of the liver and adjacent organs, etc. Complications they provoke due to uncertain malignant potential of their cells justify aggressive surgical approach.

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Sažetak

ENDOKRINI TUMOR GUŠTERAČE NEODREĐENOG PONAŠANJA: PRIKAZ SLUČAJA

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Među endokrinim tumorima gušterače koji nisu česti, veliki nefunkcionirajući tumori neodređenog ponašanja su iznimno rijetki. Nefunkcionirajući endokrini tumori gušterače proizlaze iz endokrinog dijela gušterače, ali nisu udruženi s određenim hormonskim sindromom. Opisuje se rijedak slučaj 49-godišnje žene s dobro diferenciranim endokrinim tumorom neodređenog ponašanja, koja je pri dolasku izvijestila o povremenim bolovima u epigastriju koji su se širili u desno podrebreno područje. Kompjutorizirana tomografija je pokazala dobro definiranu i omeđenu čvrstu masu u glavi gušterače. Ta masa u gušterači je kirurški odstranjena i upućena na histopatološku analizu. Mikroskopski je tumor imao relativno ujednačene stanice s ovalnim jezgrama, koje su oblagale trabekularne i pseudoglandularne strukture, te koje su također pokazale 1 mitozu na 10 VVP, dok je proliferacijska aktivnost mjerena pomoću Ki67 bila manja od 2%. Na jednom stakalcu je zapaženo središte intravaskularne invazije. Imunohistokemijske analize bile su pozitivne na NSE, kromogranin i sinaptofizin, pa je temeljem ovih nalaza, kao i veličine (promjera preko 2 cm) i utvrđene angioinvazije dijagnosticiran endokrini tumor gušterače neodređenog ponašanja. Iako se uglavnom smatraju zloćudnima, veliki nefunkcionirajući endokrini tumori gušterače mogu ponekad očitovati dobroćudno ili neodređeno ponašanje, pa stoga uvijek valja u obzir uzeti velik broj čimbenika kad se procjenjuje biološka narav ovih tumora.

Ključne riječi: *Novotvorine endokrinih žlijezda – dijagnostika; Novotvorine endokrinih žlijezda – kirurgija; Novotvorine gušterače – klasifikacija; Novotvorine gušterače – dijagnostika; Prikaz slučaja*