

CASE REPORT

Asymptomatic Calcitonin-Secreting Tumor of the Pancreas. A Case Report

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ABSTRACT

Context Pancreatic endocrine tumors are unusual tumors arising from cells belonging generically to the amine precursor uptake and decarboxylation system.

Case report We present a case of a calcitonin-secreting pancreatic endocrine tumor in a 59-year-old male who presented at our Center with elevated calcitonin values. The patient was asymptomatic. Further investigation revealed a tumor, 80 mm in diameter, in the pancreatic body and tail along with three metastatic lesions in segments III, V, and VIII of the liver. Following a distal pancreatectomy, splenectomy and wedge resection of segments III and V along with radiofrequency ablation of the segment VIII lesion, his serum calcitonin reached normal values.

Conclusions Calcitonin-secreting pancreatic endocrine tumors are often malignant and have a poor prognosis. We believe that an aggressive surgical approach may improve survival.

INTRODUCTION

Pancreatic endocrine tumors (PETs) are rare neoplasms accounting for 1-2% of all

pancreatic tumors and having a clinically recognized annual incidence of 1-5/1,000,000 [1].

The majority (65-85%) of clinically relevant PETs are functional (syndromic), while 15-35% of them are non-functional (i.e. not associated with a clinical syndrome of hormone hyper function) regardless the levels of hormone(s) in blood.

All PETs (with or without a hyper functional syndrome) can synthesize and release a variety of hormones, either the islet-type or the 'ectopic'-type, such as calcitonin.

Calcitonin-secreting PETs are extremely rare tumors with fewer than 20 cases described in the literature, mainly as isolated case reports [2, 3, 4]. We present a case of a calcitonin-secreting tumor with liver metastases which was surgically treated.

CASE REPORT

A 59-year-old Caucasian male patient presented with elevated serum values of calcitonin after a thyroid nodule was incidentally discovered. The work-up confirmed high serum calcitonin levels (129 pg/mL; reference range: 0-19 pg/mL) but failed to reveal any clinical or laboratory parathyroid or thyroid abnormality, other than a colloid nodule in the thyroid gland. It is worth mentioning that the patient was totally asymptomatic, with no diarrhea, abdominal

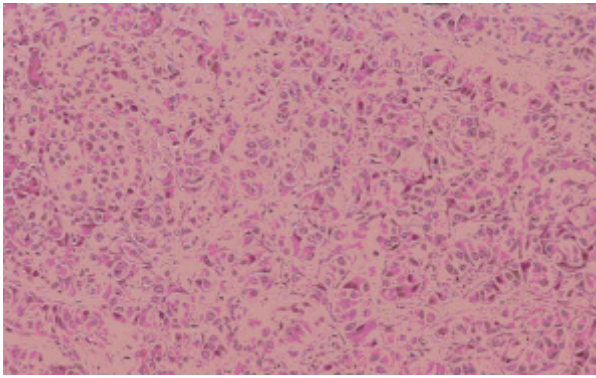


Figure 1. Calcitonin-secreting pancreatic endocrine tumor. Ribbons of neoplastic cells invade the pancreatic parenchyma. A residual islet is seen on the left side of the picture (H&E x100).

pain or flushing, which often accompany elevated serum calcitonin levels.

An abdominal CT scan revealed a tumor, 80 mm in diameter, in the pancreatic tail, extending to the body-tail junction, as well as two liver metastatic lesions located at segments III and V. The hormone profile and the tumor markers (CEA and CA 19-9) were unremarkable.

Intraoperative US exploration for a complete evaluation of the pancreas and peripancreatic regions was performed. The liver was carefully assessed for evidence of metastatic disease and the CT findings were confirmed. In addition, a new subcentimeter lesion in segment VIII was documented. Potential extrapancreatic sites of the tumor were evaluated, with particular attention being paid to the duodenum, splenic hilum, small bowel and its mesentery. No signs of invasion of the portal vein were noted.

A distal pancreatectomy with splenectomy, local excision of segments III and V of the liver and radiofrequency ablation of the hepatic lesion in segment VIII were performed.

Histopathological examination revealed a pancreatic endocrine tumor measuring 80x35 mm, composed of epithelial cells arranged in trabeculae, ribbons and solid nests. These cells exhibited moderate atypia and mitotic activity, and invaded some nerve sheaths and the adjacent pancreatic parenchyma (Figure 1). The pancreatic resection margins were free of tumor, but 4 out of the 19 peripancreatic

lymph nodes exhibited metastatic infiltration. Immunohistochemically, the tumor cells diffusely expressed calcitonin (Figure 2), neuron specific enolase (NSE), synaptophysin, chromogranin, and keratins of high and low molecular weight. No glucagon, gastrin, VIP, PP, insulin, somatostatin and somatostatin-receptor expression was noted. The resected hepatic lesions measured 12 and 15 mm in diameter and were microscopically identical to the pancreatic tumor. However, no calcitonin expression was identified but scattered cells revealed somatostatin immunoreactivity.

The post-operative period was uneventful and the patient was discharged on the 9th postoperative day. Serum calcitonin levels were decreased and were almost normal (11.3 pg/mL) on the 20th postoperative day.

No signs of recurrence were noted three months after surgery. A CT scan revealed a successfully ablated lesion in segment VIII which was also confirmed by scintigraphy with In-III (octreotide).

DISCUSSION

PETs arise from a primitive neuroendocrine stem cell, with the capacity of differentiating into various hormone-secreting cells. Many PETs are comprised of more than one hormone-producing cell type. Calcitonin immunoreactivity is usually detected in up to 20% of non-functioning tumors and in 10% of the cells, along with various other hormones [1].

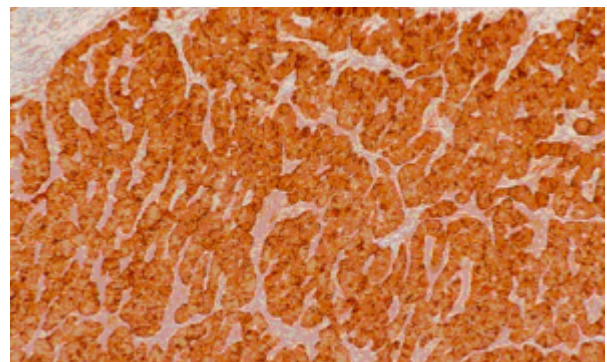


Figure 2. Intense calcitonin immunoreactivity of the tumor cells. Peroxidase-anti-peroxidase (PAP) x100.

Calcitonin is a peptide normally secreted by thyroid C cells. The role of calcitonin in the normal physiology of humans is not entirely known. This hormone has potent effects on mineral ion flux through its action on the kidneys and bone. It decreases blood calcium levels by inhibiting bone resorption and promoting renal excretion of calcium. Phosphaturia is also stimulated by calcitonin [3].

Increased levels of serum calcitonin are usually considered to be indicative of medullary carcinoma of the thyroid. However, other non-tumoral and tumoral conditions may also be associated with hypercalcitoninemia, such as renal insufficiency, acute pancreatitis, hypergastrinemia, or lung cancer, pheochromocytoma, melanoma, breast cancer and colorectal cancer [2].

Calcitonin-secreting PETs are very rare tumors with fewer than 20 cases reported in the literature, but little is known about the symptoms and the evolution of the disease in the affected patients. About half of these PETs are functional, the patients often presenting with diarrhea or flushing. Whether these symptoms are due to hypercalcitoninemia has not been elucidated [2]. In fact, many of these PETs are proven to co-secrete other peptides as well, such as VIP and somatostatin [2, 3, 4]. The remaining cases of these PETs are non-functional with some patients presenting with clinical signs of malignancy, either local or metastatic, and a few being asymptomatic, as in the case of our the patient.

Some PETs including calcitonin-secreting variants, are small in size and are thereby, difficult to evaluate. A combination of various diagnostic modalities such as CT, MRI, endoscopic ultrasound, somatostatin receptor scintigraphy, angiography and venous sampling need to be combined with a thorough exploration and intraoperative ultrasound evaluation at laparotomy [3].

Most PETs are histologically well- or moderately-differentiated. In calcitonin-secreting tumors, the percentage of the calcitonin-immunoreactive cells varies from 5 to 100% and other peptides such as

somatostatin or VIP are usually co-expressed [2, 3, 4]. The behavior of these tumors is not restricted to cytological criteria (with the exception of the small-cell, undifferentiated highly aggressive variant) but in a combination of parameters including tumor size, mitotic rate, presence of necrosis, angioinvasion and hormonal and functional status. Non-functional tumors and those producing 'ectopic' hormones have very high malignancy rates (more than 75% and 90-100%, respectively). Malignancy is typically determined by the presence of local invasion, spread to regional lymph nodes, or the existence of hepatic or distant metastases [5, 6].

Most reported calcitonin-secreting PETs are malignant. The patients usually present with a mainly hepatic metastasis and have an unfavorable outcome. Liver metastases are a major prognostic factor in patients with calcitonin-secreting PETs. The progression of liver metastases is also an important factor which must be taken into account when deciding on the therapeutic approach. The only other independent prognostic factors in PETs are tumoral cell differentiation (small cell vs. non-small cell types) and complete resection of the primary tumor [5].

The goals of surgical therapy for PETs include control of the symptoms from hormone excess, safe resection of the maximal tumor mass and preservation of the maximal pancreatic parenchyma. Management strategies, including preoperative, intraoperative and postoperative considerations, vary for the different types of endocrine neoplasms. Some calcitonin-secreting PETs are larger than 2 cm, and are not safely excised using local techniques. Tumors in the head, neck or uncinata process of the pancreas typically require pancreaticoduodenectomy for safe resection, while tumors arising in the body or tail are treated by distal pancreatectomy. Surgical resection for metastases is only possible in less than 10% of affected patients, hence other palliative procedures, such as hepatic artery embolization and ablation therapies, have been used [7, 8]. In a recent study, the

authors concluded that complete surgical resection is the only curative treatment for endocrine tumors, including hepatic resection in selected cases [8]. However, surgical resection must be safe and associated with a low morbidity and mortality and should therefore be performed in specialized centers. The normalization of calcitonin values post-operatively indicates disease eradication, as was noted in the current case, although liver metastasis did not reveal calcitonin immunoreactivity.

There is no definite data which indicate that serum calcitonin levels can be used as a tumor marker in predicting the outcome of patients. There is a high plasticity of the mechanisms controlling endocrine cell differentiation in PETs, with frequent direct switching of a specific hormone-producing cell to a different hormone-producing (even ectopic) cell; therefore, it is not unusual for metastatic lesions to secrete hormones different from their primaries, as it was noted in the current case.

CONCLUSIONS

Calcitonin-secreting PETs are extremely rare tumors. Fifty percent of patients with this kind of tumor are non-symptomatic; therefore, the diagnosis is based on incidental findings. In patients with calcitoninemia and absence of medullary cancer of the thyroid, the possibility of a calcitonin-secreting PET should be suspected. Liver metastasis is a dismal prognostic factor in patients suffering from the disease. Calcitonin-secreting tumors are often malignant and have a poor prognosis. Although experience is limited due to the rarity of calcitonin-secreting PETs, we believe that an aggressive surgical approach may improve survival and alleviate symptoms of the disease.

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Keywords Calcitonin; Endocrine Gland Neoplasms; Pancreatic Neoplasms

Abbreviations PET: NSE: neuron specific enolase; pancreatic endocrine tumor

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