



CASE REPORT

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Incidental intraoperative discovery of a pancreatic neuroendocrine tumor associated with chronic pancreatitis

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Abstract

Pancreatic neuroendocrine tumors are a rare entity with an incidence between 2 per million to 5 per 100 000. Association with pancreatitis (acute or chronic) is rare and is considered to be determined by the tumoral obstruction of pancreatic ducts, but sometimes occurs without any apparent relationship between them. Non-functional neuroendocrine pancreatic tumors are usually diagnosed when either very large or metastatic. Small ones are occasionally diagnosed when imagery is performed for other diagnostic reasons. Intraoperative discovery is even rarer and poses problems of differential diagnosis with other pancreatic tumors. Association with chronic pancreatitis is rare and usually due to pancreatic duct obstruction by the tumor. We describe the case of a patient with a small non-functioning neuroendocrine tumor in the pancreatic tail accidentally discovered during surgery for delayed traumatic splenic rupture associated with chronic alcoholic pancreatitis. The tumor of 1.5cm size was well differentiated and confined to the pancreas, and was resected by a distal splenopancreatectomy.

Conclusions: Surgeons should be well aware of the rare possibility of a non-functional neuroendocrine tumor in the pancreas, associated with chronic pancreatitis, surgical resection being the optimal treatment for cure. Histopathology is of utmost importance to establish the correct diagnosis, grade of differentiation, malignancy and prognosis.

Virtual slides: The virtual slide(s) for this article can be found here: <http://www.diagnosticpathology.diagnomx.eu/vs/2114470176676003>.

Keywords: Pancreatic neuroendocrine tumor, Chronic pancreatitis, Splenopancreatectomy

Background

Pancreatic neuroendocrine tumors are a rare entity, part of a larger group called gastroenteropancreatic endocrine tumors, with histologic origins in the neuroendocrine cells inside the pancreas [1].

Incidence ranges from 1–2 cases per million individuals [2] to 2.5–5 cases per 100000 [3] and it will probably grow more due to availability of modern and powerful diagnostic tools. Incidence in autopsies ranges between 1.6% and 10% [4].

Association with pancreatitis (acute or chronic) is rare and is considered to be determined by the tumoral

obstruction of pancreatic ducts, but sometimes occurs without any apparent relationship between them [5].

Case presentation

A 58 years old patient was admitted in our surgical department for faintness and dizziness after a fall from standing occurring a week before. Known as a heavy alcohol consumer, he was frequently brought in hospital because of staggering in the streets. He denied any personal medical or surgical antecedents and couldn't indicate any family medical history. He worked as farmer all his life and had a history of smoking around 20 cigarettes per day for 10 years but stopped 8 years ago. Physical examination was normal, laboratory data within normal range excepting a mild anemia. Abdominal ultrasonography diagnosed a 100/25 mm subcapsular hematoma on the posterior side

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and a 10 mm thick fluid collection on the medial side of the spleen. There was no free fluid, nor other lesion of parenchymal viscera. The initial decision was for conservative management, patient's status improving in the following days. Third day after admission, the patient presented diffuse abdominal pain, cold sweats, tachycardia over 100/min and falling blood pressure. There was a strong suspicion of delayed splenic rupture and the patient was immediately taken to operating room.

At laparotomy there were free fresh and old blood clots in the peritoneal cavity and around the spleen, in quantity estimated up to 700–800 ml and a ruptured subcapsular hematoma on the posterior side of the spleen with active bleeding from an irregular-shaped mid-splenic fracture of 3 cm depth. No other lesions were found. Dissection of splenic vessels for vascular control, revealed a chronic pancreatitis with peripancreatic fibrosis and a 1.5-2 cm tumor palpated in the pancreatic tail right in front of the splenic hilum. The tumor had a slightly more consistency than the pancreas. There were no enlarged lymphnodes around in this area. A splenopancreatectomy was decided then with a margin of at least 3 cm proximally. The patient had an uneventful postoperative course.

Gross and microscopic examination revealed, in the pancreatic fragment attached to the spleen, a 1.5 cm nodular, well circumscribed, firm, grayish tumor, unhomogenous, with hemorrhagic foci on section.

Microscopic examination revealed a tumor incompletely delineated by a thin fibrous capsule (see Figure 1a). Tumor cells presented a pattern predominantly pseudoglandular, consisting of polygonal cells with moderate eosinophilic cytoplasm and round-oval nuclei with relatively uniform shape and size (see Figure 1b). Small hemorrhagic foci were observed in the tumor (see Figure 1c). There was no vascular or perineural invasion, nor necrosis. Number of mitosis observed was low: 2–3 mitosis /10 high power fields (400x).

Figure 1 - (a) Neuroendocrine pancreatic tumor (adenocarcinoma) well delineated by a pseudocapsule, hematoxylin eosin (100x); (b) - Pseudoglandular pattern, hematoxylin eosin (200x); (c) - Haemorrhagic foci and variable fibro-collagen stroma, hematoxylin eosin (100x).

Immunohistochemical stainings revealed tumor cells positive for chromogranin, synaptophysin, and neuron specific enolase (see Figure 2a, 2b, 2c). Proliferation markers as MIB-1 (directed against the Ki-67 antigen), were expressed in less than 2% of the tumor cells nuclei (see Figure 2d).

Figure 2 - (a) Intense and diffuse immunostaining of the tumor cells cytoplasm for Chromogranin, LSAB technique (400x); (b) - Diffuse immunostaining of the tumor cells cytoplasm for Synaptophysin, LSAB technique (200x); (c) - Immunostaining of the tumor cells cytoplasm for NSE, LSAB technique (200x); (d) - Rare Ki-67 positive neoplastic cells, LSAB technique, (400x).

Based on those characteristics (proliferating tumor confined to the pancreatic tissue, reduced size, and low proliferation index, absence of necrosis, no vascular or perineural invasion) the tumor was diagnosed as well differentiated with benign behavior according to the WHO classification [6]. 8 lymph nodes were examined and, apart from the presence of different degrees of histiocytosis, no tumoral involvement was found.

Discussion

Generally there are two categories of pancreatic neuroendocrine tumors: functional, releasing in the peripheral blood active hormones responsible for a specific clinic syndrome and non-functional, secreting either a functionally inert hormone or in very small amounts, therefore not producing any clinical symptoms [7,8].

The proportion of non-functional tumors varies largely in published series. A review by Ito et al. found 48% of pancreatic neuroendocrine tumors as non-functional [9].

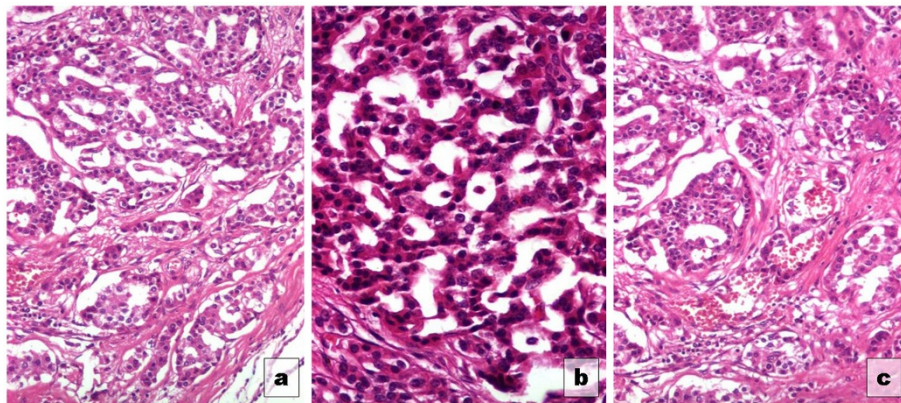


Figure 1 Histological profile of the studied tumor.

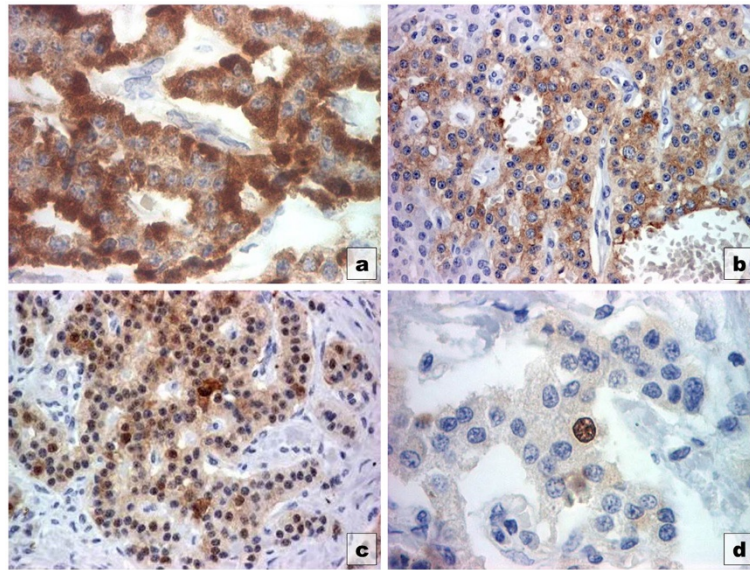


Figure 2 Immunohistochemical profile of the studied tumor.

Kazanjian et al., in a series of 70 consecutive resected neuroendocrine tumors of pancreas found 71% of them non-functional [10].

The peak incidence for these tumors is between 30 and 60 years of age [11]. Early clinical diagnosis of non-functional pancreatic tumors is very rare because usually they become symptomatic only when they grow larger or metastasize. Otherwise they are discovered incidentally on the occasion of imagistic tests performed for other medical reasons. In our case, there is a very rare situation of intraoperative discovery.

Abdominal ultrasound was performed before surgery but, on regular examination, PNETs present a hypoechoic aspect that cannot be differentiated from other types of tumor, and could escape detection because of operator's inexperience, flatulence, obesity, deep situations and locations in the tail [12]. In the case we describe the old and organizing blood clots around the spleen surely contributed to hide the tumor.

Intraoperative discovery poses problems of diagnostic and therapeutic decision. Association with a grossly aspect of chronic pancreatitis raises the suspicion of pancreatic cancer. Pancreatic neuroendocrine tumors represents less than 3% from pancreatic tumors [13,14]. It is far more rare than pancreatic adenocarcinoma, with a ratio of 1:25 [6] being substantially rarer than adenocarcinomas and carrying a better prognosis [8]. Most neuroendocrine tumors of pancreas are located in the pancreatic head [15]. In our case the tumor was located near the splenic hilum.

In front of an accidentally discovered pancreatic tumor we had to decide whether to perform or not a frozen biopsy. Due to the fact that the tumor was well confined to

the pancreas and relatively easy amenable to resection, there were no enlarged lymphnodes in the vicinity and the pancreas presented a firm consistency, well suitable for suture with low-risk for pancreatic fistula, a resection with safe margins was decided.

We think that in such cases a frozen section could not have brought any elements to change our decision. In neuroendocrine tumors of pancreas the only reason to perform a frozen section is when an enucleation is planned but even in such situations there could be problems of differential diagnosis with papillary tumors [16].

The mainstay of treatment for neuroendocrine tumors of pancreas is surgical resection. However, particularly for non-functional tumors, it remains controversial as to whether resection alters their natural history. Tumor enucleation can be performed in cases in which the pancreatic endocrine tumor is single, capsulated, of limited size (less than 2 to 3 cm) and peripheral, situated at a distance from the main duct [13,14]. The safe margin of resection is not clearly indicated in the literature. If the tumor is macroscopically well delimited the margin can be very narrow, from few millimeters to 1 cm [16].

Immunohistochemistry is of outmost importance for the study of neuroendocrine tumors of pancreas. Several antibodies are available against neuroendocrine markers such as NSE, CD56, synaptophysin, CgA, and other hormones. It is important to discriminate well-differentiated forms from poorly differentiated carcinomas using malignancy markers [17]. The malignant or metastatic potential of neuroendocrine pancreatic tumors can be estimated using the tumor size, mitotic index, expression of KI-67 protein, vascular invasion, and perineural invasion [18]. The proliferation marker MIB-1 (directed against

the Ki-67 antigen) helps to determine tumor grade and prognosis [3].

Association with pancreatitis (acute or chronic) was already reported in the literature. Mostly, there are reports of acute pancreatitis generated by obstruction of the main duct by the tumor [5,19,20]. In some of the cases the acute pancreatitis became chronic. In other, there was no evident relationship between chronic pancreatitis and the neuroendocrine tumor [5]. In 71% of the cases the tumor was malignant [19].

In our case the association between chronic pancreatitis and PNET seemed purely incidental because the pancreatitis involved grossly the entire pancreatic gland and the tumor was located in the proximity of the splenic hilum. In addition, the patient was a chronic alcohol consumer, a well-known etiological factor for chronic pancreatitis.

There are very few studies in the literature searching a common genetic pathway for chronic pancreatitis and pancreatic neuroendocrine tumors. In an interesting comparative study in search for specific molecular markers, Bloomstone et al. [21] compared them with different other pancreatic diseases as chronic pancreatitis and pancreatic adenocarcinomas. They found that ELOVL4 (a gene codifying the protein for the elongation of very-long-chain fatty acids 4-like, responsible for the biosynthesis of fatty acids) and CALCR (gene responsible for calcitonine receptor) were increased both in neuroendocrine tumors and chronic pancreatitis.

Overall prognosis after resection is much better than of other pancreatic tumors. In a review of 3851 cases, survival was 59.3% at 5 years and 37.7% at 10-years. Age, grade, distant metastases, tumor functionality, and type of resection were independent predictors of survival, meanwhile gender, race, socioeconomic status, tumor size, nodal status, margins, adjuvant chemotherapy, and hospital volume had no influence [22].

Beside association with chronic pancreatitis, there are reports of a unique association between carcinoid tumors and renal cell carcinoma in a mature cystic teratoma of a horseshoe kidney. In this case the tumor presented also a low grade of malignancy and differentiation as adenocarcinoma as in our case [23]. Primary renal carcinoid tumors are morphologically and histologically similar to those in other sites. The surgical resection is curative and prognosis is good in the absence of metastasis but long term follow-up is recommended because distant recurrence may occur up to seven years postoperatively [23].

Immunohistochemical markers may be related also with prognosis beside their diagnostic role. Expression of NSE and CD 56 was studied in renal cell carcinoma and was correlated with prognosis. First of all, NSE marker was exhibited by 48% of the renal cell carcinoma in a series of 152 cases. In the same series there was an 18% of CD56

positive stain. Renal cell carcinomas that exhibited NSE and/or CD56 had a poorer prognosis.[24].

Conclusions

Incidental intraoperative discovery of a neuroendocrine adenocarcinoma is a rare event that may arouse important diagnostic issues and therapeutic decisions. Association with chronic alcoholic pancreatitis is also rare and not fully understood. Histopathology and particularly immunohistochemical stains remain crucial for the diagnosis in respect of malignancy and prognosis.

Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

LSAB: Enzyme-labeled streptavidin-biotin; WHO: World Health Organisation; MIB-1: Marker for cell proliferation, directed against the nuclear Ki-67 antigen; NSE: Neuron specific enolase; CD56: Equivalent NCAM (neural cell adhesion molecule); CgA: Chromogranin A.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

VS and SR contributed to acquisition of data, conception and drafting of manuscript. MG performed histologic and immunohistochemical analysis and provided results. EP reviewed the manuscript and gave final approval of the version to be published.

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