Case report

A RARE LARGE CYSTIC TUMOUR OF PANCREAS – A CASE REPORT AND LITERATURE REVIEW

Running Title: Cystic Pancreaic Neuroendocrine tumour

KEY WORDS

Cystic pancreatic neuroendocrine tumours

Mucinous cystic neoplasm

Intraductal papillary mucinous neoplasm

LIST OF ABBREVIATION:

PanNETs – Pancreatic neuroendocrine tumours

MCN – Mucinous cystic neoplasm

IPMN – Intraductal papillary mucinous neoplasm

CBD – Common bile duct,

MPD – Main pancreatic duct,

SMA/SMV – Superior mesenteric artery/vein

EUS – Endoscopic ultrasound scan

Abstract:

Introduction:Cystic Pancreatic Neuroendocrine tumours (Pan NETs) are rare entities, which pose diagnostic challenges. Their clinical and pathological charecteristics are not well understood.

Case report: Here with we are presenting a 62 yrs old patient, who presented with vague abdominal symptoms and was subsequently found to have large cystic lesion arising from the head of pancreas, compressing the portal and superior mesenteric vein. She underwent pylorus preserving pancreatico-duodenectomy. Histology confirmed grade III pancreatic neuroendocrine tumour. No postoperative complications and received adjuvant chemotherapy.

Discussion: There are conflicting reports to suggest whether they are due to necrosis/degneration of solid PanNETs or a distinct group of tumour with different charecteristics. Size varies from 1-18 cm and sometimes difficult to differentiate from MCN/IPMN. Preoperative diagnostic accuracy is very low. Surgical resection is the treatment of choice

Conslusion: Cystic PanNETs are a distinctive subgroup of PanNETs with unique clinical and pathologic features. Awareness and proper recognition will help in their diagnosis. Resection is the treatment of choice. Further genetic/molecular studies will broaden the treatment options.

Introduction:

Pancreatic neuroendocrine tumors (PanNETs) are typically solid neoplasms but in rare instances may present as cystic lesions. This unusual presentation can make clinical diagnosis challenging. In addition, the clinical and histopathologic characteristics of cystic PanNETs are poorly defined.

Similar to solid PanNETs, cystic PanNETs develop with an equal sex distribution and over a wide age range (23 to 91 y; mean, 52 y). The unusual cystic appearance make radiologic differentiation from other cystic pancreatic neoplasms difficult with a misdiagnosis. Here with we present a case of

successfuly treated large cystic neuroendocrine tumour of the pancreas.

Case report:

62 years old pleasant lady presented to us with colicky abdominal pain over a period of 2 months. She has no significant past medical history apart from peuperal sterilisation. She consulted a GP outside and was treated as dyspepsia. Since her symptoms did not improve after few weeks she consulted another doctor, who organised an ultrasound scan. The ultrasound scan showed a large cystic lesion in the abdomen, probably arising from the pancreas. Because of this finding – she was referred to us.

On clinical examination, she was obese with stable vitals. There was no pallor, jaundice, generalised lymphadenopathy. Abdominal examination showed palpable mass in the right hypochondrium. We organised a CT scan of chest, abdomen and pelvis.

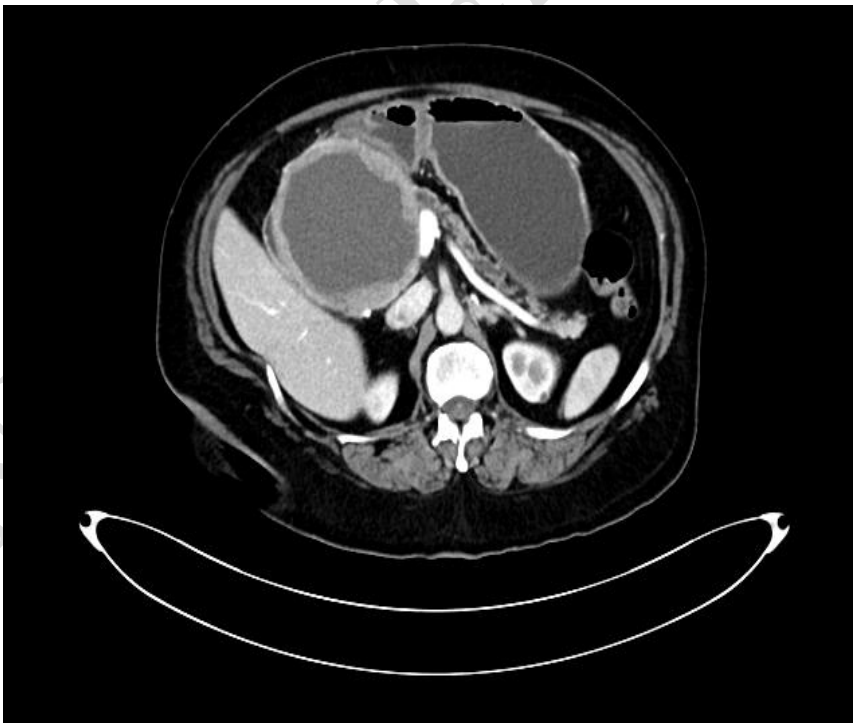

Fig 1. Large cystic lesion at the head with atrophic pancreas and dilated duct

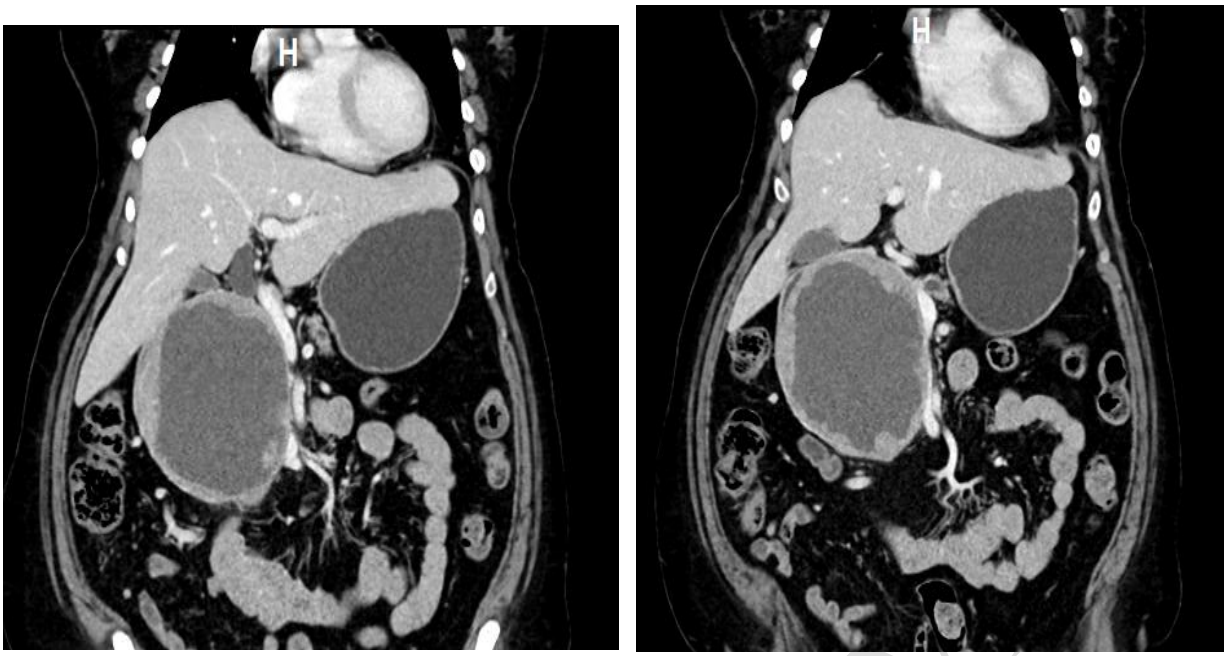

Fig 2: Large cystic lesion of pancreas compressing portal and superior mesenteric vein

CT scan of the abdomen showed - There is well-defined hypodense lesion with irregular enhancing wall (upto 1.3 cm thick) is seen in the head and uncinate process of the pancreas, measuring 10 x 10.3 x 12 cm (Figure 1). No calcification / enhancing septa / scar. In the medial aspect the lesion causes significant narrowing of portal vein/SMV (approximately 9cm) with loss of fat plane (Figure 2). SMA is seen separately. The lesion causing mass effect over the proximal CBD causing upstream dilation of CBD (diameter 1.5 cm) and central intrahepatic biliary radicals. CT chest – did not reveal any distant metastases. All her labs including CA19-9 levels, were with in normal limits. With the provisional diagnosis of mucinous cystic neoplasm – she was counselled for whipple's procedure. Patient and family were explained about the procedure and informed consent obtained.

Procedure:

She had initial laparoscopy – to rule out peritoneal disease. Then her abdomen was opened with roof top incision. Intraoperative findings as follows:

- Large cystic lesion arising from the head of the pancreas compressing PV and SMV
- Large branch from SMV supplying the lesion – required resection and suturing the defect in SMV

- Mesocolon adherent to the cystic lesion – middle colic vessels ligated
- Thin walled gall bladder with multiple stones and dilated CBD
- Firm pancreas with dilated MPD (4-5mm)
- few hepato-dudoenal lymphnodes.
- Paraumbilical hernia – omentum as a content
- No evidence of liver/peritoneal metastases or free fluid in the abdomen

Patient underwent successful pylorus preserving pancreatico duodenectomy (PPPD). Eventhough the portal vein and SMV were adherent to the tumour, they were released completely without any oncological compromise (Figure 3) and the whole tumour was removed (Figure 4). Standard reconstruction was performed.

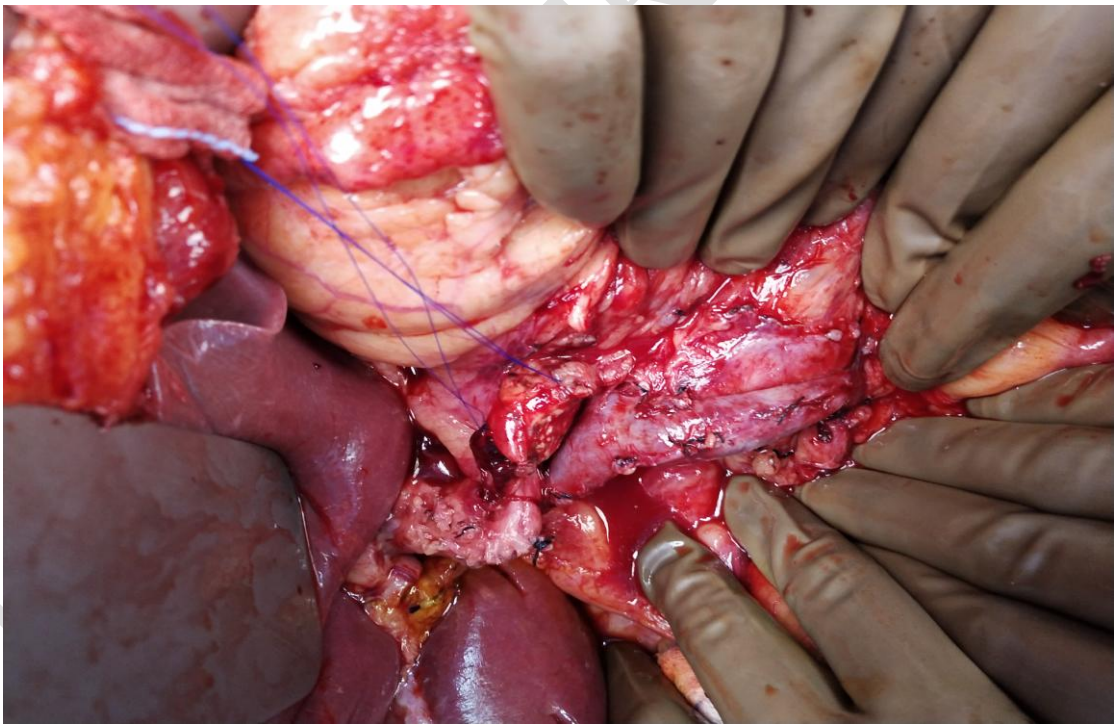

Fig 3. Intraoperative picture showing released PV/SMV/SV

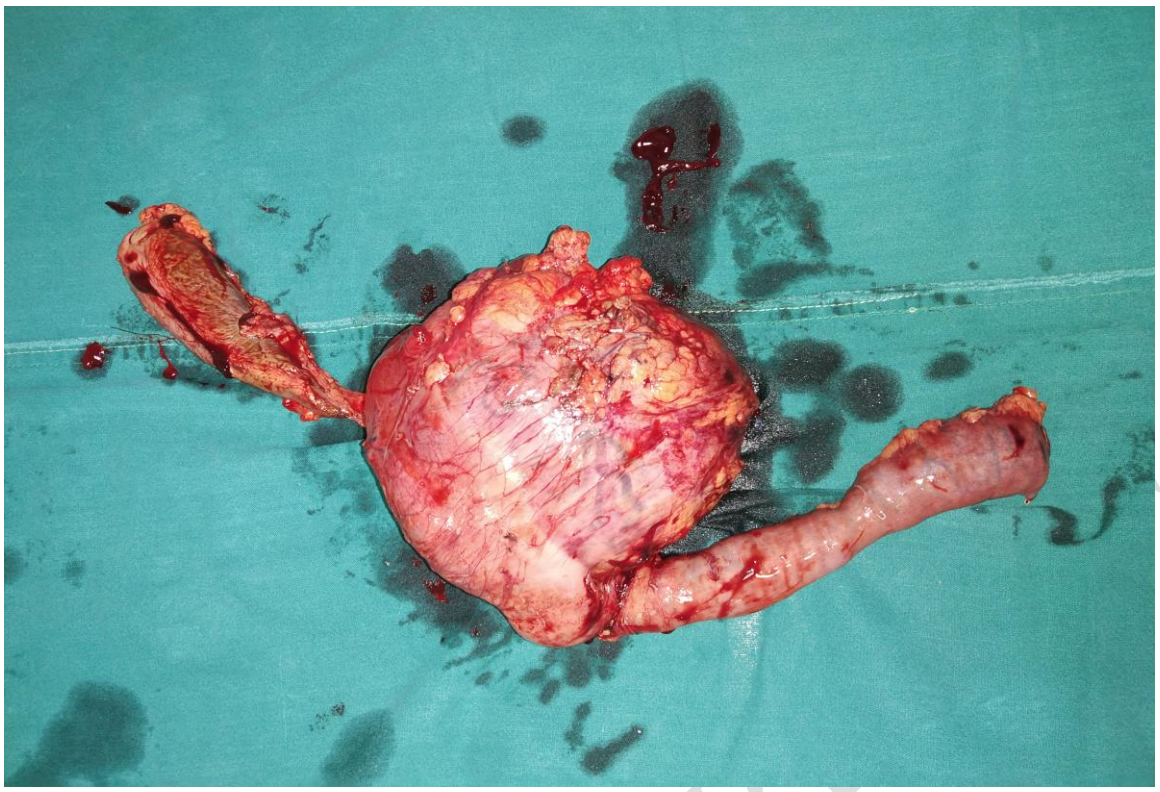

Fig 4. Resected specimen

Histology:

Pathological examination shows a tumor in the head of pancreas. The tumor is encapsulated with a thick capsule and focal capsular dehiscence involved by tumor. The tumor is composed of sheets, trabeculae and acinar pattern of arrangement with delicate rich vascular network. The cells are relatively uniform and show finely granular amphophilic to eosinophilic cytoplasm, centrally located round to oval coarsely clumped nucleus with distinct nucleolus. Mitosis upto 3/2 mm2 is seen. Tumor necrosis, haemorrhagic areas are seen and central areas show cystic degeneration with cystic and hemosiderin laden macrophages. All margins clear of tumour. 21 lymphnodes found and were free of tumor.

Immuno Histo Chemistry Markers

Synaptophysin	**:**	**Immunoreactive in tumor cells (3+)**
Chromogranin	**:**	**Immunoreactive in tumor cells (3+)**
NSE	**:**	**Immunoreactive in tumor cells (3+)**
CD-56	**:**	**Immunoreactive in tumor cells (3+)**
Pan CK	**:**	**Immunoreactive in tumor cells (2+)**
Ki-67	**:**	**24 %**

Impression: **Neuroendocrine tumour (Pan NET, G3)**

Her postoperative period was uneventful and she was succesfully discharged on Day 6. Her case was discussed in tumour board and decided for adjuvant therapy. She received adjuvant chemotherapy. On 18 months follow up with PET-CT imagings – she is doing well with no evidence of recurrence.

Discussion:

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms that comprise up to 5% of pancreatic malignancies. These neoplasms have an estimated incidence of 4 to 5 individuals per 100,000 per year in the United States.[1] However, their incidence is increasing, likely due to advancements and increased use of radiographic and endoscopic imaging.[2] The classification of PanNETs is complex and generally subdivided into either functional (hormone secreting) or nonfunctional. In addition, tumor size and histologic grade, as defined by the proliferation rate, are prognostically important. The majority of PanNETs are nonfunctional and, as a result, frequently go undiagnosed until late in their clinical course. Although PanNETs are typically solid, in rare instances these tumors present as cystic lesions. Grossly the size vary from 1cm to 18 cm. It is generally assumed that cystic PanNETs are the result of tumor necrosis within solid PanNETs. Thus, they are thought to be similar in biological behavior and malignant potential to their solid counterparts. But conflicting reports suggest that cystic PanNETs represent a distinct entity rather than a morphologic variant. In fact, several studies have found cystic PanNETs to be more frequently associated with multiple endocrine neoplasia type 1 (MEN-1) and less aggressive than their solid counterparts. [3-5]

Since its original description by Thigpen in 1940, [6] subsequent studies have been conflicting as to whether cystic PanNETs represent a distinct biological entity or are formed by necrosis and degeneration. The etiology of cystic PanNETs remains controversial, and several theories have been put forth. 1) Slow-growing PanNETs develop a fibrous capsule that eventually restricts the blood supply to the tumor, resulting in infarction and necrosis. 2) Cystic change or necrosis correlated with large tumor size 3) Hemorrhage within the tumor is the inciting event in cyst development. 4) Alternatively, cyst development may be related to an FNA. 5) Exomic sequencing has identified a subset of PanNETs with recurring mutations in MEN-1, DAXX/ATRX, and the mTOR pathway. Thus, it is not unreasonable to assume that an underlying genetic etiology may be responsible for cystic PanNETs. [7]

Cystic PanNETs were typically sporadic (91%), nonfunctional (91%), solitary (87%), and were discovered incidentally (62%). In comparison with their solid counterparts, cystic PanNETs were more frequently found in the tail (53% vs. 36%). In addition, cystic PanNETs were less likely to demonstrate tumor necrosis, perineural invasion, vascular invasion, regional lymph node metastases, and synchronous distant metastases compared with solid PanNETs. Prognostically, they presented at a lower pathologic stage using both the AJCC and ENETS systems and decreased Ki-67 proliferation index compared with solid PanNETs. However, whether these prognostic predictors are valid for cystic PanNETs remains to be proven [7].

Although some studies have reported that cystic PanNETs could be identified preoperatively by a hypervascular rim, accurate preoperative diagnosis of cystic PanNETs was reported to be only 23% [8]. MR may perform better than CT for detecting ductal communication in pancreatic cysts, that usually is not considered as a cystic pancreatic neuroendocrine tumors feature [9]. The relatively low resolution of cross sectional imaging compared with EUS precludes the ability to separate cystic PNETs from other cystic neoplasms [10,11]. Concurrently, the improvement in endoscopic techniques has allowed nonsurgical sampling and evaluation by endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-guided FNAB). Due to the high rate of diagnostic accuracy and low rate of complications, EUS has become an integral part of the preoperative assessment of pancreatic cysts. The most important advantage with endoscopic ultrasound is the possibility to obtain tissue and fluid samples from the cysts helpful for the assay of tumour markers such as CEA, enzymes like amylase, molecular markers and cytology. All of these are essential for the achievement of a correct preoperative diagnosis and an appropriate tumor management. [9]

The primary difficulty was distinguishing cystic PanNETs from other cystic neoplasms of the pancreas such as IPMN or MCN. As the clinical management for different cystic neoplasms of the

pancreas varies, preoperative diagnosis is of utmost importance. Both main duct-IPMNs and MCNs can be associated with an invasive ductal adenocarcinoma [12-14] Recent exomic sequencing of PanNETs has identified a subset of tumors harboring mutations within the mammalian target of rapamycin (mTOR) pathway [15] The mTOR pathway inhibitor, everolimus, has been shown to increase progression-free survival in a subset of PanNET patients [16] Hence, in the future, patients with PanNETs may be treated with targeted therapies inappropriate for IPMNs and MCNs.

Since the cystic PanNETs pose diagnostic challenge it is advisable to resect these lesions. Their high resectability rate supports the role of surgical approach and complete resection is actually the treatment of choice for cystic PNETs. Accurate preoperative diagnosis is important for patient management as “watch-and-wait” approach could be highly risky in patients with pancreatic mass lesions.

In summary, cystic PanNETs are a distinctive subgroup of PanNETs with unique clinical and pathologic features. Because of their cystic nature, these neoplasms often present a diagnostic dilemma to both the experienced radiologist and pathologist. Awareness and proper recognition of these entities including their associated findings can aid in their diagnosis. Resection is the treatment of choice. Future genetic and molecular studies should help shed light on the pathogenesis and possible treatment strategies for these neoplasms.

References:

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–3072.
2. 2. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9:61–72.
3. Boninsegna L, Partelli S, D'Innocenzio MM, et al. Pancreatic cystic endocrine tumors: a different morphological entity associated with a less aggressive behavior. Neuroendocrinology. 2010;92: 246–251.
4. Bordeianou L, Vagefi PA, Sahani D, et al. Cystic pancreatic endocrine neoplasms: a distinct tumor type? J Am Coll Surg. 2008;206:1154–1158.
5. Ligneau B, Lombard-Bohas C, Partensky C, et al. Cystic endocrine tumors of the pancreas: clinical, radiologic, and histopathologic features in 13 cases. Am J Surg Pathol. 2001;25:752–760.
6. Thigpen FMA. Pathologic Study of Cysts of the Pancreas. Rochester, MN: University of Minnesota; 1940.
7. Aatur D. Singhi, , Linda C. Chu, w Armanda D. Tatsas, Chanjuan Shi, Trevor A. Ellison, Elliot K. Fishman, Satomi Kawamoto, Richard D. Schulick, Christopher L. Wolfgang, Ralph H. Hruban, and Barish H. Edil. Cystic Pancreatic Neuroendocrine Tumors A Clinicopathologic Study (Am J Surg Pathol 2012;36:1666–1673)
8. L.R MCKenna, B.H. Edil. Update on pancreatic neuroendocrine tumors. Gland. Surg., 3 (4); 2014: 258-275
9. Cagli a et al. Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge. International Journal of Surgery, 21;2015: 44-49.
10. BK Goh, LL. Ooi, YM Tan, et al. Clinico-pathological features of cystic pancreatic

endocrine neoplasms and comparison with their solid counterparts. Eur.J. Surg. Oncol. 32 (2006): 553-56

11. SA Ahrendt, RA Komorowski, MJ Demeure, SD Wilson, HA Pitt. Cystic pancreatic neuroendocrine tumors: is preoperative diagnosis possible? J. Gastrointest. Surg. 6(2002): 66-74.
12. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449:395–401.
13. Thigpen FMA. Pathologic Study of Cysts of the Pancreas. Rochester, MN: University of Minnesota; 1940.
14. Crippa S, Salvia R, Warshaw AL, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247:571–579.
15. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011;331:1199–1203.
16. Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol. 2010;28:69–76.