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Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge

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ABSTRACT

Objective: Cystic PNETs are an uncommon neoplasms increasingly detected in current clinical practice which often present a diagnostic challenges to both the experienced radiologist and pathologist. The aim of this study was to review the available literature to summarize current data that compare and evaluate both the clinical and pathologic features of cystic pancreatic neuroendocrine tumors.
Materials and methods: A systematic review of the current literature was performed using the search engines EMBASE and PubMed to identify all studies reporting on cystic pancreatic neuroendocrine tumors. The MeSH search terms used were "cystic pancreatic neuroendocrine tumors", "endocrine neoplasms", and "pancreatic cysts". Multiple combinations of the keywords and MeSH terms were used.
Results: The clinical evaluation of cystic pancreatic lesions appears to suffer from same limitations despite the improvement in the diagnostic tools. Subsequently, we highlight diagnostic pitfalls and differential diagnosis of these cystic tumors. In this review we discuss current advances in the application of the imaging modalities and characteristics features with special emphasize on endoscopic ultrasound (EUS), and EUS guide fine needle aspiration (EUS-FNA).
Conclusions: Cystic neuroendocrine tumor in the pancreas underlines the clinical impact of endoscopic ultrasound in the work-up of patients with unclear lesions in the pancreas. EUS-FNA cytology and cyst fluid analysis is a useful adjunct to abdominal imaging for the diagnosis of pancreatic cystic lesions. Due to the evident diagnostic difficulties, we hypothesize that cyst fluid characteristics, including cytomorphological features, is the most accurate test to achieve a preoperative diagnosis and to provide a basis for prognostic prediction.

1. Introduction

Pancreatic cystic lesions, classified as cystic neoplasms, solid neoplasms with cystic change, or non-neoplastic cysts are being increasingly detected during the last years and have become a common incidental finding in clinical practice [1]. Solid pancreatic tumors with cystic changes such as solid pseudo-papillary tumors, rarely adenocarcinoma and its variants, also include the pancreatic neuroendocrine tumors [2,3].

Pancreatic neuroendocrine tumors (PNETs), previously referred to as islet cell tumors, are rare subgroup of pancreatic tumors and represent 1–5% of all pancreatic neoplasms [1–10]. However, autopsy studies have found the prevalence of PNETs ranges from 0.8% to 10%, suggesting that the vast majority of them are clinically silent. The majority of PNETs arise sporadically but approximately 10% are associated with a genetic syndrome such as multiple endocrine neoplasm (MEN) type I and von Hippel-Lindau disease (VHL) [11–13]. Poorly understood for many years, there have been a number of recent advances in our understanding of these tumors.

The history of classification and staging of PNETs has undergone a great number of changes in the last 10–15 years. Currently, the WHO, European Neuroendocrine Tumor Society (ENETS), and

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American Joint Committee on Cancer (AJCC) have each proposed a formal staging system for PNETs [13,14]. In the European Neuroendocrine Tumor Society (ENETS) consensus guidelines, the grading of proliferative rate of the tumor cells based on combination the mitotic rate and Ki-67 labeling index is advocated [15]. Moreover, the newest World Health Organization (WHO) classification incorporates grading and staging, and provides a basis for prognostic prediction [16]. These grading systems are helpful to assess the predictive malignant potential in the patients with pancreatic NETs. The seventh edition of the AJCC prognostic staging system also emphasized the malignant potential of all of these lesions [17] and some clinical or pathological features of poorly differentiated PNENs have been widely established.

Histologic grade, as defined by the proliferation rate measured by mitotic count and the expression of nuclear antigen Ki-67, large tumor size, irregular surface, peritumoral vascular invasion and distant metastasis are therefore considered prognostically important [15,16,18,19]. It would be expected to apply more practically the classifications listed above, but some controversial issues in the preoperative diagnoses of the pancreatic NETs still remain. The classification of PNETs is complex and generally subdivided into either functional or non-functional, although the clinical relevance of this distinction has recently been questioned as the treatment of these tumors follow the same general principles [20].

Pancreatic neuroendocrine tumors may manifest at any age, but they most often occur in the 4th to 6th decades of life, with no sex predilection, rarely seen in children and adolescents [21,22]. The majority of PNETs are non-functional and, as a result, frequently go undiagnosed until late in their clinical course [23]. During recent years it appears that there is an increase in the incidence of these tumors, probably as the result of several factors such as the widespread use of high-resolution abdominal imaging, the increase in the awareness and recognition of these tumors and the improvement in pathological diagnosis involving immune-histochemical staining for specific neuroendocrine tumor markers [9,24].

Pancreatic neuroendocrine tumors although are typically solid, in rare instances present as cystic lesions. However, the increasing number of diagnostic examinations enable more often detect cystic lesions of the pancreas, and cystic pancreatic neuroendocrine tumors (cystic PNETs) thus represent to date a real diagnostic challenge.

Cystic PNETs, once thought rare, account for a large percentage of PNETs, whit a reported proportions between 13% and 17% [25–28].

Grossly, cystic PNETs may have a variable from small to large size [29] and usually the cysts do not communicate with the pancreatic ducts. As expected from their gross appearance, cystic PNETs were well circumscribed and surrounded by a thin to thick fibrous capsule. The typically cytopathological features are the classic endocrine morphology of polygonal cells with plasmacytoid appearance, admixed with fragments of neoplastic cells. The cells showed uniformly sized round to slightly oval nuclei and coarse stippled chromatin provided sufficient evidence of an endocrine neoplasm. Cyst fluid is clear to straw-colored and thin in consistency. In larger lesions may be present hemorrhage within the cyst [2,29].

It is generally assumed that cystic PNETs are the result of tumor necrosis within solid PNETs. Thus, they are thought to be similar in biological behavior and malignant potential to their solid counterparts [27,30]. But conflicting reports suggest that cystic PNETs represent a distinct entity rather than a morphologic variant [25,31,32].

Predominantly cystic PNETs were more commonly located in the neck, body or tail of the pancreas than in the head compared with solid counterpart.

The aim of this study was to review the available literature to summarize current data that compare and evaluate both the clinical and pathologic features of cystic pancreatic neuroendocrine tumors. In this review we discuss current advances in the application of imaging modalities and characteristics features with special emphasize on endoscopic ultrasound (EUS), and EUS guide fine needle aspiration (EUS-FNA). Due to the evident diagnostic difficulties, we hypothesize that cyst fluid characteristics, including cytomorphological features is the most accurate test to achieve a preoperative diagnosis and to provide a basis for prognostic prediction.

2. Clinical features

Even though PNETs are slow growing and are not as aggressive as carcinomas. Most PNETs display an indolent course of disease and usually are well differentiated tumors. Most patients are asymptomatic on presentation, producing symptoms only as a consequence of tumor growth and the invasion of adjacent structures or tumor metastases [9,11]. Most nonfunctional PNETs present in fact symptoms such as abdominal or back pain, weight loss, severe weakness, anorexia, obstructive jaundice, palpable mass, nausea and emesis, pancreatitis [32]. As mentioned before, about 10% of PNETs are functional and the presenting symptoms depend on the particular hormone that is being produced. Nonfunctional PNETs, however, frequently secrete a number of other substances, for instances, chromogranins, neuron-specific enolase, subunits of human chorionic gonadotropin, neurotensin, and grehlin, but these hormones are not secreted or do not lead to a clinical syndrome [7,8,33]. Detection of many tumor markers have been proposed for functional and non-functional pancreatic neuroendocrine tumors. However the specificity of these markers reaches almost 100% [34], the sensitivity of these tumor marker, individually assessed, is rather low [35].

Once a pancreatic cyst is detected, is important to categorize the cyst as benign, pre-malignant or malignant in order to avoid unnecessary surgical resection. A detailed history and clinical examination is essential in these patients. The clinical history should focus on signs of tumor mass or metastasis, evaluate for symptoms of an associate endocrine syndrome and screen for family history suggestive of genetic syndromes. A decreased proportion in the trend for surgical treatment of pancreatic cystic lesions in the recent years thanks to the improved preoperative diagnostic techniques was showed in an interesting case series of surgical resection [36]. If a functional syndrome is suspected, workup should include a targeted biochemical evaluation.

3. Imaging

Localization and staging of the lesion is essential to appropriate therapy for pancreatic neuroendocrine tumors. A variety of imaging modalities exist to assist the clinician, including computed tomography (CT), magnetic resonance (MR), somatostatin receptor scintigraphy (SRS), positron-emission tomography (PET), endoscopic ultrasound (EUS) and angiography with selective arterial stimulation and venous sampling in case that the tumor cannot be located. Cystic PNETs can mimic other cystic pancreatic masses on imaging studies, posing a diagnostic challenge to radiologists. CT is the most common initial imaging study in the evaluation of the patients with cystic pancreatic lesions. Limited data are available for a detailed analysis of the CT appearance of cystic PNETs. Cystic PNET is often is a component of a large tumor with cystic degeneration or necrosis [37,38]. They usually appear as a cystic lesions that rarely obstruct the pancreatic duct, with smooth margins and peripheral enhancement usually on both arterial and portal phases

because of their rich blood supply [37]. Although it varies with the size of the lesion, the reported sensitivity of CT ranges from 62 to 83% with a specificity of 83–100% [39,40]. The usefulness of CT for the evaluation of cystic pancreatic lesions remains an understudied topic primarily because of the multiple advantages of MR imaging relative to CT in the characterization of these lesions, however, recently published data suggest that the role of CT can be comparable and complementary to that of MR imaging [41,42].

MR, because of its superior fluid and soft-tissue contrast, affords the best non-invasive means for the morphologic evaluation of cystic lesions of the pancreas. The MR signal is typically low in T1-weighted sequences, and high in T2-weighted sequences. As reported the sensitivity and specificity of MR ranges from 75 to 100% [43,44]. Not as commonly used as CT, MR is most often ordered when lesions are too small to be visualized on CT. MR has been suggested to be superior to CT in detecting and following liver metastases [45,46].

SRS uses radiolabeled somatostatin analogs and relies on somatostatin receptors expressed by PNETs. Insulinomas, in which somatostatin receptors are absent or however present only at low levels, are not well visualized with this technique. For other functional and non functional PNETs the ability of SRS to localize the tumor is good, with sensitivities ranging from 75 to 100% [44,47]. SRS is also typically useful in evaluating the metastatic spread.

Due to the low metabolic rate which involves well histological differentiation, standard PET imaging with 18F-Fluorodeoxyglucose (FDG) does not visualize PNETs optimally. However, it can detect poorly differentiated PNETs and FDG avidity correlates with early tumor progression. Alternatively, PET imaging has increasingly utilized 68Ga labeled somatostatin analogs with excellent results [48–51].

EUS combines both endoscopic and ultrasounds examination into a single modality and has become an indispensable diagnostic technique in the evaluation of pancreatic lesions. Internal positioning of the probe allows high-resolution imaging of organs and surrounding structures adjacent to the gut lumen. Cystic PNETs usually appear as well-circumscribed lesions either completely cystic or with solid and cystic components, thus showing a nonspecific morphology at EUS. Endoscopic ultrasound offers the additional benefit of obtaining biopsies and cyst fluid examination providing additional pathological findings. A concentration of carcinoembryonic antigen (CEA), at a level of >192 ng/ml, allowed accurate characterization for differentiating mucinous from non-mucinous cystic lesions [52], while CEA and amylase concentrations are noted to be low in case of cystic pancreatic neuroendocrine tumors. Occasional increased CEA expression in neuroendocrine tumor of the pancreas should be related with multilineage differentiation [53–56]. Cytology may also diagnose malignant cystic lesions by demonstrating cells with high grade atypia or neoplastic in the cyst fluid increasing the diagnostic yield of EUS-guided FNA. EUS has an 82% sensitivity and a 92% specificity in identifying PNETs, although EUS is more sensitive in the head of the pancreas than the tail, where predominantly are localized the cystic pancreatic neuroendocrine tumors, thus resulting operator dependent [57,58]. The overall complication rate of EUS-FNAB appears to be 1–2%. The reported complications are infections, bleeding, pancreatitis, and duodenal perforation [59]. Cystic pancreatic lesions appear to have a greater risk of infectious complications than solid pancreatic masses.

4. Discussion

The recognition of cystic pancreatic lesions has increased in the last decade, owing in part to improved abdominal imaging [60,61]. Pancreatic cyst is not a rare medical entity and their prevalence has been estimated to range from 2 to 24% in imaging and autopsy studies [62,63]. Recent series reported that more than 50% are neoplastic lesions and constitute about 10–15% of all neoplasm in the pancreas [64–66]. Pancreatic cystic neoplasms are composed of a heterogeneous group of tumors and are widely variable in term of their malignant potential, ranging from benign and indolent neoplasms to invasive carcinomas. Separating cystic pancreatic lesions with malignant potential from those typically associated with a benign clinical course is an important clinical distinction with respect to treatment. Some of them are benign lesions and can be safely managed expectantly, and some others are pre-malignant or malignant lesions and generally require surgical resection at diagnosis or close follow up. Decisions regarding surgical treatment of cystic lesions of the pancreas are based on the potential risk of malignancy or the presence of symptoms [67]. On the other hand, surgical resection of all pancreatic lesions, particularly those located in the pancreatic head, is associated with a significant morbidity [68]. Therefore, approaching a patient with pancreatic cyst, whether congenital, inflammatory or neoplastic, poses a significant diagnostic challenge. Relatively common cystic tumors, classified by world health organization (WHO) [13], are serous cystadenomas (SCAs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs). In addition, primary solid pancreatic tumors such as ductal adenocarcinoma, acinar cell carcinoma, and pancreatic neuroendocrine tumors can be observed with cystic features and, while rare, have been reported [69,70].

Although the cytomorphological features of solid PETs have been well characterized, those of their cystic counterparts have received little attention. Cystic PNETs were classically considered very rare, however, recent studies suggest that these particular pancreatic lesions may be more common than previously thought [71]. First described by Thigpen in the1940s [29], one of the main challenges in the management of cystic PNENs is establishing an accurate preoperative diagnosis. Cystic PNETs were typically solitary, nonfunctional and were incidentally discovered. In comparison with their solid counterparts, cystic PNETs were more frequently found in the tail of the pancreas. Using both the AJCC and ENETS systems they usually present a lower pathologic stage and decreased Ki-67 proliferation index compared with solid counterpart. However, whether these prognostic predictors are valid for cystic PNETs remains to be proven [29]. It is presumed that these typically solid neoplasms are secondarily cystic, but the question has been raised whether cystic PNETs represent a distinct biological entity or are formed by necrosis and degeneration variant [32]. However the cause of cyst formation of cystic PNET remains controversial, and several hypotheses have been proposed [3,27,32,72,73]. Preoperative radiologic diagnosis of cystic PanNETs continues to be a challenge even though using a multidisciplinary and multimodal approach. A peripheral hypervascular rim is considered the radiologic feature most suggestive of cystic PNETs but multiple features of peripheral contrast enhancement on CT evaluation were reported. Especially in the small pancreatic neuroendocrine tumors, thickness of the peripheral contrast enhancement could be thin-to-medium or thin-to-thick. Occasionally may be focally thickened with a crescentic appearance and often smooth in those prevalently cystic [25,74].

A potential limitation on CT evaluation is that peripheral contrast enhancement may be seen only transiently. Small tumors are occasionally seen only on either arterial or portal venous phase images. Peripheral contrast enhancement was often observed more clearly on the arterial phase than on the venous phase, but always is visualized on the arterial phase [75–77]. Although some studies have reported that cystic PNENs could be identified preoperatively by a hypervascular rim, accurate preoperative diagnosis of cystic

PNENs was reported to be only 23% [32]. Moreover tumors may be mischaracterized as a nonspecific cystic tumor if the pancreas is not scanned during the phase of predominant contrast enhancement and the peripheral enhancing component may appear isodense to surrounding pancreatic parenchyma. Thus an accurate pancreas protocol is essential to detect peripheral contrast enhancement to avoid this misinterpretation on CT evaluation. Magnetic Resonance little add to the diagnostic definition, in fact the diagnostic accuracies for making the correct histologic diagnosis in pancreatic cysts of computed tomography (CT) and magnetic resonance (MR) are comparable ranging from 40 to 60%. 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 [41,78,79]. The relatively low resolution of cross-sectional imaging compared with EUS precludes the ability to separate cystic PNETs from other cystic neoplasms [27,72]. 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 [53,80] EUS has become an integral part of the preoperative assessment of pancreatic cysts and many Authors supports the value of EUS over CT/MRI in the evaluation of pancreatic cysts, because of its high resolution and easy access to the cyst for FNA [28,52,81]. However the occurrence of complications such as bleeding, pancreatitis, and infection is more frequent in cystic lesions than in solid lesions. Furthermore tumor seeding may occur more frequently in mucinous cystic lesions, especially those located in the body or tail of the pancreas thus prompting care when performing EUS-FNAB for pancreatic cystic lesions [82]. Although any unique endoscopic ultrasound finding in cystic neuroendocrine tumors was reported [83], others authors have suggested that cystic neuroendocrine tumors exhibit more frequently a thick wall compared to mucinous cysts [28]. Anyhow, the most important advantage with endoscopic ultrasound is the possibility to obtain tissue and fluid samples from the cysts helpful for the assay of tumor markers as carcinoembryonic antigen, enzymes as amylase, molecular markers and cytology [10,52,84,85], all of these essential for the achievement of a correct preoperative diagnosis and an appropriate tumor management [61,86].

5. Conclusions

Cystic PNETs are an uncommon neoplasm increasingly detected in current clinical practice, which often present a diagnostic challenges to both the experienced radiologist and pathologist. Cystic PNETs represent a subgroup of pancreatic cystic and neuroendocrine tumors, difficult to diagnose preoperatively because the majority of these are nonfunctional, with varying malignant potential even if biologically less aggressive as compared with their solid counterparts. Their high resectability rate supports the role of surgical approach and complete resection is actually the treatment of choice for cystic PNETs. In our opinion accurate preoperative diagnosis is important for patient management as “watch-and-wait” approach could be highly risky in patients with pancreatic mass lesions. However, preoperative diagnosis of these lesions can sometimes be difficult at CT and MR imaging and may require additional evaluation. Cystic neuroendocrine tumors have in fact imaging features over lapping with those of other pancreatic cysts lesions and those features are often insufficiently accurate for the preoperative diagnosis. Differential diagnosis includes simple cysts, other cystic neoplasms, pseudocysts and adenocarcinomas with cystic degeneration. Endoscopic ultrasound (EUS) and fine-needle aspiration (FNA) has enabled not only the detailed examination of pancreatic cystic lesions but cyst fluid analyses may provide additional cytology and immunohistochemical information and should be integral parts of a multidisciplinary diagnostic approach to the evaluation of patients with cysts of the pancreas. This finding may provide critical information essential to the preoperative planning and decision-making on the appropriate surgical strategy for cystic PNETs. Use of a multidisciplinary approach, early diagnosis, and accurate classification of cystic lesions of the pancreas will lead to improved patient outcomes.

Ethical approval

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Author contribution

Pietro Caglià: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Maria Teresa Cannizzaro: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Angelo Tracia: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Luca Amodeo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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Antonino Buffone: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Corrado Amodeo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Matteo Angelo Cannizzaro: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflicts of interest

The authors have no conflict of interest or any financial support.

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