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Original research

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