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Cystic pancreatic neuroendocrine tumours — a gastroenterologist's point of view

Neuroendokrynne torbielowate nowotwory trzustki — punkt widzenia gastroenterologa

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Abstract
Cystic pancreatic tumours are detected with increasing frequency and remain a clinical problem. Because they have varying potential of malignancy the management and decision-making process is a hard task. Guidelines concerning pancreatic cystic tumours indicate management with mucinous, serous cystic pancreatic neoplasms and solid pseudopapillary tumours, while the management with pancreatic cystic neuroendocrine tumours is not included into these standards. This review tries to find out whether cystic pancreatic neuroendocrine tumours are different entities from solid tumours of neuroendocrine origin. The management and differential diagnosis of these neoplasms with special focus on features on imaging studies allowing preoperative diagnosis are discussed. **(Endokrynol Pol 2018; 69 (3): 320–325)**

Key words: *neuroendocrine pancreatic tumors, pancreatic cysts, EUS*

Streszczenie
Torbielowate guzy trzustki są coraz częściej wykrywane w badaniach obrazowych i stanowią problem kliniczny. Charakteryzują się różnym potencjałem transformacji w guzy złośliwe, dlatego też postępowanie z tego typu zmianami jest trudnym zadaniem. Wytyczne dotyczące guzów torbielowatych trzustki odnoszą się głównie do torbielowatych nowotworów surowiczych, śluzowych i guza pseudobrodawkowatego, podczas gdy postępowanie z torbielowatymi guzami neuroendokrynnymi trzustki nie zostało w nich uwzględnione. W prezentowanej pracy autorzy próbują odpowiedzieć na pytanie, czy torbielowate guzy neuroendokrynne trzustki mają odmienną biologię niż guzy lite, przedstawiają również postępowanie oraz diagnostykę różnicową tych zmian, ze szczególnym uwzględnieniem charakterystyki torbielowatych nowotworów neuroendokrynnych w badaniach radiologicznych i endosonograficznych pozwalających na postawienie przedoperacyjnej diagnozy. **(Endokrynol Pol 2018; 69 (3): 320–325)**

Słowa kluczowe: *guzy neuroendokrynne trzustki, torbiele trzustki, EUS*

Introduction

The numbers of detected pancreatic cystic neoplasms are increasing. Management with these lesions is a challenge and often a dilemma because they carry varying potential of malignancy. Moreover, pancreatic surgery, especially pancreatoduodenectomy, is connected with a high morbidity (postoperative complications present in 50% of patients), and a significant number of deaths (about 5%) [1–3].

International guidelines concerning the management with cystic pancreatic tumours recommend management with mucinous and serous cystic neoplasms (MCN, SCN), solid pseudopapillary tumours (SPN), and are not focusing on pancreatic cystic neuroendocrine tumours (CPEN) [4, 5]. CPENs are often misdiagnosed on imaging studies, but these lesions are neoplasms we should be aware of and take into account during differential diagnosis of cystic pancreatic tumours [6]. Moreover, making a false diagnosis can have serious consequences, especially in CPENs that are more than 2 cm in size, which is an indication for surgery according to the Polish Network of Neuroendocrine Tumours and European Neuroendocrine Tumour Society guidelines [7, 8]. In this review, we try to answer to the question: Is the biological behaviour of pancreatic cystic neuroendocrine tumours different from solid ones? We especially focus on features of pancreatic cystic neuroendocrine tumours on imaging studies allowing for the proper preoperative diagnosis.

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Epidemiology of pancreatic cystic neoplasms and pancreatic neuroendocrine cystic tumours

Neuroendocrine tumours and pancreatic cystic lesions are detected with increasing frequency [9]. Pancreatic cysts are found in 20% of magnetic resonance imaging (MRI) and 1.2–2.6% of computed tomography (CT) scans [4, 10–12]. The prevalence increases with age, and in autopsy studies they are detected in 24.7% of patients [13]. Most pancreatic cysts are either non-neoplastic lesions, like pseudocysts, or tumors with low (SCA), intermediate (IPMN-BD — branch duct intrapappilary mucinous neoplasma or higher potential of malignant transformation (MCN — mucinous cystic neoplasma, IPMN-MD — main duct intrapappilary mucinous) neoplasms, SPN — solid pappilary neoplasms). Pancreatic neuroendocrine tumours (PNEN) constitute about 5% of all pancreatic neoplasm with increasing incidence of 0.32/100,000/year [7, 14]; among these, cystic lesions represent from 13 to 17% of all PNENs [15–17]. In the study by Bordeianou et. al. CPENs constituted 7–8% of all resected pancreatic cysts, but this diagnosis was preoperatively suspected in a minority of patients [18–20]. These cystic lesions are probably more prevalent because most of the studies focus only on CPNENs after surgery; thus, many of the tumours probably remain undetected or misdiagnosed. CPENs are usually diagnosed in the 5th and 6th decade of live with equal sex distribution and in 44% of cases are found incidentally [21, 22].

Clinicopathological features and comparison between solid and cystic neuroendocrine tumours

It is a matter of a debate whether the CPENs represent just a variant of solid tumour or a different entity. It is suspected that they appear as a result of haemorrhage, necrosis, disturbances of the blood supply caused by the tumour capsule, intraductal growth, or cystic degeneration of solid PNENs [17, 22]. However, there are a lot of clinical differences between solid and cystic neuroendocrine tumours [16]. In contrast to solid NENs, more common location of CPENs is distal pancreas rather than pancreatic head [17]. Cystic tumours are also larger and more often symptomatic than solid PNENs [16, 17]. It is worth mentioning that the presence of the cystic component correlates with the tumour size, and its extent is associated with better prognosis [18, 23, 24]. Moreover, CPNENs are generally less aggressive than solid NENs, taking into account not only lymph node distant metastases, but also histopathological features like perineural and vascular involvement, presence of necrosis, mitotic count, and Ki67 proliferation index [6, 17]. There are discrepancies between the researchers concerning the issue of prognosis. In the largest comparative studies of Bordeianou et al. and Koh et al. there was no significant difference in five-year survival between solid and cystic neuroendocrine tumours [17, 18]. However, in the study of Paiella et al. on 46 resected CPNETs, the tumours were well differentiated (G1, G2-less likely) and there was no lesion with Ki67 index over 5% [25]. Another proof of relatively indolent behaviour is the retrospective analysis of Cloyd et al., in which there were no cases of purely cystic neuroendocrine tumours with metastases, recurrence, or death caused by the disease in patients after surgery [24]. It should also be mentioned that CPNENs are typically less likely to produce hormones and they are more commonly associated with MEN1 syndrome than their solid counterparts [18, 24]. Von Hippel-Lindau disease should be also taken into account when the diagnosis of CPNEN is made [26, 27]. The most common type of functional tumour in both solid and cystic NENs is insulinoma [22].

Management with pancreatic cystic malignancies

The whole clinical picture should be taken into account when the diagnosis of cystic pancreatic neoplasm is made. It should include: patient's age, sex, presence of symptoms, location of the lesion, pattern on imaging, results of biopsy, and the presence of so-called "high risk stigmata" or "worrisome features' [4]. All of the cystic neoplastic lesions have some potential of malignancy, which is high for mucinous tumours such as mucinous cystadenoma and intraductal papillary mucinous neoplasms, main duct type (IPMN-MD), intermediate for intraductal papillary mucinous neoplasms, brunch duct type (IPMN-BD), and low for SCA. The CT and MRI (according to the European experts consensus statement) remain a basic modality allowing for the assessment of the lesion, its resectability, and the presence of metastases, while endoscopic ultrasound (EUS) remains part of a 'multi-modality diagnostic evaluation' [5]. The EUS and EUS-FNA (fine-needle aspiration) should be performed when we suspect that it would change our management [5, 28]. According to the international guidelines it is indicated when, so-called "worrisome features" are found, i.e. size > 3 cm, thickened walls, presence of mural nodules, dilation of the pancreatic duct, lymphadenopathy, fast growth of the lesion, or elevation of serum Ca19.9 marker [4]. However, the results of EUS and biopsy do not always allow a final preoperative diagnosis. Moreover, the limitation of the assessment of tumour morphology alone (without biopsy) in EUS is its relatively low overall diagnostic

accuracy allowing a diagnosis in 50–73% of cases [5]. Furthermore, the disadvantage of EUS-FNA is often insufficient material obtained for cytopathological and biochemical analysis [5, 29]. EUS with biochemical cyst fluid analysis allows for differentiation between mucinous, serous, and non-neoplastic lesions with specificity of 88% and sensitivity of 63% [5, 30]. Therefore, we are not always able to make a final diagnosis of cystic pancreatic lesions preoperatively. The surgery is indicated, according to European guidelines, in MCN, IPMN-MD, and SPT, while in SCA a conservative approach is the method of choice [5]. In BD-IPMN indications for surgery include: dilation of pancreatic duct > 6 mm, presence of mural nodule, and or clinical symptoms, otherwise follow-up is indicated [5]. It should be noted that pancreatic surgery, even in tertiary centres, is associated with significant death and complication rates, which makes the management with cystic tumours a dilemma [31].

Pancreatic cystic neuroendocrine tumour on radiological imaging and endoscopic ultrasound

Pancreatic neuroendocrine tumours are typically solid tumours with peripheral enhancement and increased vascularisation on ultrasound Doppler imaging and CT scan [21]. CPENs should be suspected when cysts with arterial and venous enhancement are found in CT [18, 32]. CPENs in CT scan are mostly mixed solid-cystic lesions, and according to a study by Kawamoto et al. a minority of the lesions (17.8%) are predominantly cystic [32]. Calcifications are rare but can be present [21]. However, a few analyses showed that there are no characteristic features of CPNENs allowing for preoperative diagnosis in CT scan [33]; thus, EUS might be helpful in establishing a final diagnosis. The study by Khasab et al. showed increased diagnostic yield and accuracy of EUS over CT and MRI in presurgical prediction of cystic pancreatic lesions [34]. Unfortunately, there is no unique appearance of CPENs in EUS, and patterns observed in the examination include: cystic or mixed solid-cystic lesions, and unilocular or microcystic tumour with or without septations [26, 35]. The only ultrasound feature that is present more frequently in EUS, in comparison to mucinous cysts, is the presence of thick wall and well-defined margins of the lesion [26, 35]. The superiority of EUS over CT or MRI is the possibility to assess small lesions and to perform biopsy with cytological and biochemical analysis of fluid [36]. In the study by Morales-Oyarvide et al. biopsy allowed for a proper presurgical diagnosis in a significant proportion (77%) of patients [19]. Examples of EUS images of cystic pancreatic neuroendocrine tumour from our

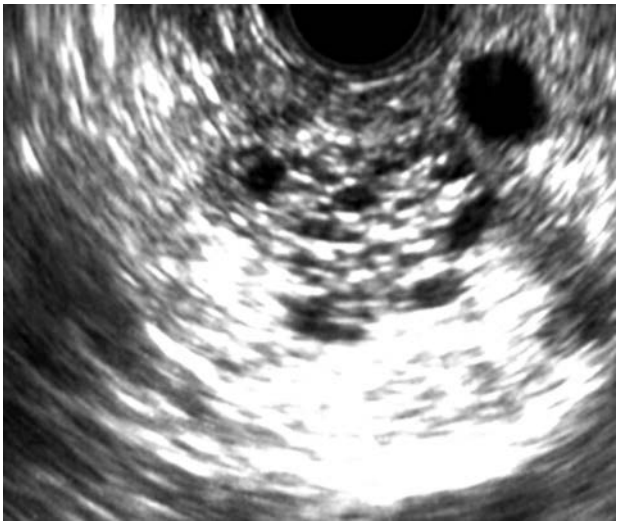

Figure 1. *Endoscopic ultrasound of microcystic neuroendocrine tumour of the pancreatic head in a 43-year-old woman. The tumour mimics cystic serous adenoma. The diagnosis of neuroendocrine origin of the lesion was made on the pathological assessment of material obtained during surgery. Biopsy under EUS guidance was inconclusive*

Rycina 1. *Endoskopowa ultrasonografia mikrotorbielowatego neuroendokrynnego mikrotorbielowatego guza głowy trzustki u 43-letniej kobiety. Guz przypomina torbielakogruczolaka surowiczego. Ostateczna diagnoza została postawiona na podstawie oceny patomorfologicznej materiału pooperacyjnego. Biopsja pod kontrolą EUS nie była wystarczająca do postawienia rozpoznania*

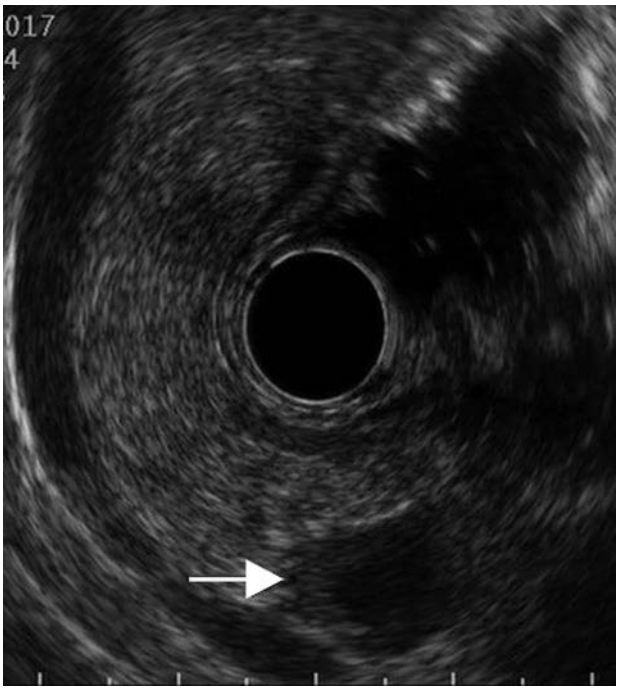

Figure 2. *EUS of a 37-year-old patient with MEN1 syndrome shows a cystic pancreatic tail neuroendocrine tumour with characteristic thin wall*

Rycina 2. *Badanie EUS u 37-letniej pacjentki z zespołem MEN1 — uwidoczniono zmianę w ogonie trzustki z typową dla guzów neuroendokrynnych pogrubiałą ścianą*

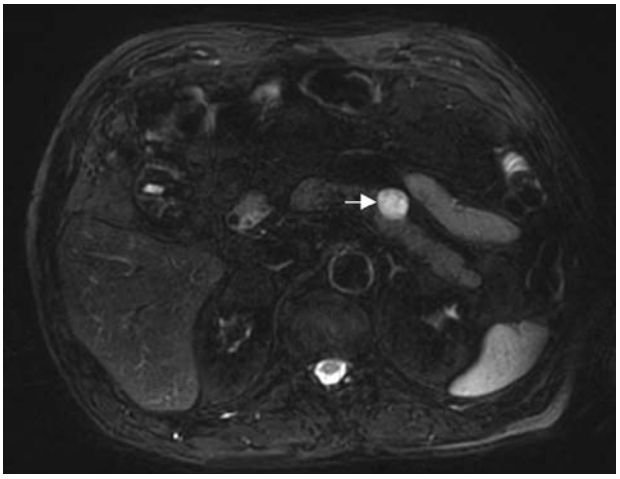

Figure 3. *MRI, T2-weighted image of a 60-year-old man with a cystic neuroendocrine tumour of the pancreatic body (NET G1) manifesting as hyperintensive lesion. The tumour was found incidentally*

Rycina 3. *MRI, obraz T2-zależny, przypadkowo znaleziona hiperintensywna zmiana torbielowata u 60-letniego mężczyzny (NET G1)*

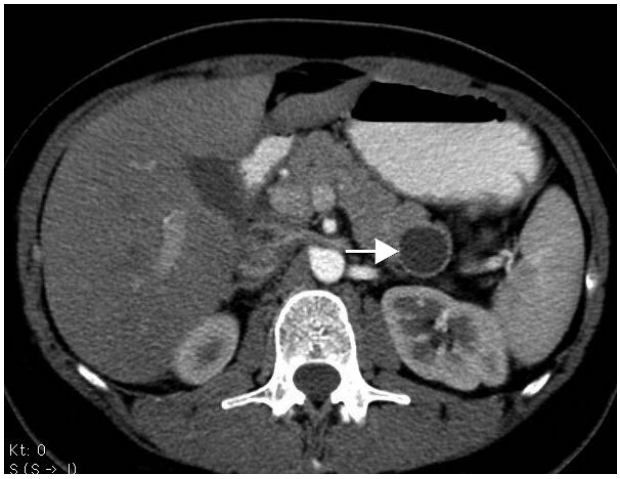

Figure 4. *Abdominal CT scan of a 31-year-old woman with a cystic neuroendocrine tumour of the pancreatic tail*

Rycina 4. *Tomografia komputerowa u 31-letniej pacjentki z neuroendokrynnym guzem torbielowatym ogona trzustki*

department are presented in Figure 1 and 2. CT and MRI images are presented in Figure 3 and 4.

Differential diagnosis

Despite our knowledge of cystic and neuroendocrine tumour biology and guidelines we have at our disposal, making a presurgical and final diagnosis of cystic pancreatic tumour is not always possible. The limitations are the sensitivity and specificity of imaging methods and biopsy (see chapters above). CPNENs are often misdiagnosed on imaging studies [6]. The differential diagnosis of CPNENs includes mainly mucinous tumours (IPMN, MCN), solid pseudopapillary tumour, cystic metastases to pancreas, cystadenocarcinoma, and atypical (not honeycomb pattern) serous cystadenoma, which can be similar to CPNEN not only in CT scan but also in scintigraphy [37]. The biggest challenge (due to different clinical management) is to properly diagnose patients with CPNENs and qualify patients with lesions > 2 cm to surgery. The mistake that should be avoided is misdiagnosing CPEN with branch duct IPMN and then to treat the patient conservatively. International guidelines define branch duct IPMN as a "pancreatic cysts > 5 mm in diameter that communicate with the main pancreatic duct", and typically it resembles a bunch of grapes [4, 21]. CPENs, in contrast to IPMN-BD, typically do not communicate with the pancreatic duct [5, 6]. Furthermore, on imaging studies (with use of CT/MRI) only 33% of CPNENs had high-risk stigmata and 18% had worrisome features, which, judging only on these modalities, could convince us to treat CPNENs conservatively [19]. EUS has become an important diagnostic tool and a valuable part of the multimodal approach to pancreatic cystic lesions. However, this modality, in terms of diagnosing cystic pancreatic tumours, has its limitations. According to the study of Morales-Oyarvide et al. the diagnosis of CPNEN was suspected in EUS only in 47% of post-operatively confirmed cases [19]. The results of cystic pancreatic fluid analysis were also not conclusive. Fluid analysis in CPNENs showed low viscosity and low levels of CEA (in contrast to mucinous tumours) and amylase [19, 21]. In contrast to serous cystadenoma, CPNENs have low or absent glycogen content in fluid aspirate [21]. However, currently used markers do not allow a final diagnosis to be made, and new markers of CPNENs are being sought. In the study of Oruc et al. cystic fluid levels of chromogranin A(CgA) (non-specific serum marker of neuroendocrine tumours) were not characteristic for CPNENs and did not have any value in the differential diagnosis of pancreatic cystic lesions [38]. In contrast to the abovementioned methods, EUS-FNA with cytological examination of cells is the more specific method when CPEN is suspected. In the studies of Morales-Oyarvide et al. and Singhi et al. cytological analysis allowed a proper diagnosis in 77% to 84% of cases [19], and in the study of Yoon et al. diagnostic positive cytology was more frequent in patients with CPNENs than in those with mucinous cysts [19]. Typically, CPENs are composed of polygonal, plasmacytoid looking cells with round or oval and slightly peripheral nuclei, nodular, dull, "salt and pepper' chromatin, and positive staining for chromogranin A and synaptophysin

[6, 19, 26]. The possibility of obtaining positive cytology is significantly higher in patients with CPNENs than in those with mucinous cystic neoplasms [26]. Therefore, EUS-FNA with cytological analysis and staining for neuroendocrine tumour markers should be performed whenever CPEN is suspected [36]. Postoperative histopathological differential diagnosis should include especially solid pseudopapillary tumour and acinar cell carcinoma [6, 39].

How should we manage pancreatic cystic pancreatic neuroendocrine tumours?

As was mentioned, the preoperative and definitive diagnosis of pancreatic cystic tumours is often a hard task, and cystic lesions are often incorrectly classified [17]. Cystic pancreatic tumour should be suspected when a cystic or mixed solid-cystic tumour with peripheral enhancement is found in CT scan and/or cystic tumour with thick walls is seen in EUS. In such cases EUS with FNA should be performed. When the diagnosis of neuroendocrine tumour is made we should follow the guidelines concerning the solid tumours and follow-up the tumours that are no more than 2 cm in size. Patients with larger lesions should be referred to a surgeon. However, we should take into account and evaluate the hormonal activity and remember that neuroendocrine tumours with cystic component have less aggressive behaviour than solid ones [17]. This fact is of great importance in older patients with comorbidities. Furthermore, when surgery is indicated, more conservative surgery types (enucleation, spleen preserving distal pancreatectomy) should be considered [17].

Summary

We can conclude that cystic PNENs probably represent a different entity than solid tumours, which we should be aware of in differential diagnosis of pancreatic cystic tumours. These tumours have different clinical characteristics; therefore, the presence of a cystic component should be taken into account in decision making processes in patients with pancreatic neuroendocrine tumours. The limitations of the presented data are the relatively small groups of patients included in the studies and the fact that analysis focused on patients after surgical resections.

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